CLINICAL NEUROSURGERY





Wilder Graves Penfield M.D

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Preface

This fourth volume of *Clinical Neurosurgery* contains the edited proceedings of the Sixth Annual Meeting of The Congress of Neurological Surgeons held in Chicago, November 1–3, 1956

The Congress of Neurological Surgeons takes great pleasure and is privileged in dedicating this volume to Doctor Wilder Penfield, this year's honored guest and speaker Each previous annual meeting has honored an outstanding senior neurosurgeon as the Society's guest speaker—1952, Professor Herbert Olivecrona, Stockholm, Sweden, 1953, Sir Geoffrey Jefferson, Manchester, England, 1954, Doctor Kenneth McKenzie, Toronto, Canada 1955, Doctor Carl Rand, Los Angeles, California.

The format of this volume is much the same as in previous proceedings The papers, except those of Doctor Penfield, are devoted to the various neurological aspects of the pituitary region The contributors to this volume are all men of considerable experience and are authorities in their particular field.

The editors extend their sincere appreciation to the program committee and officers of The Congress of Neurological Surgeons, to the contributors, and last but not least, to the publisher Only because of the excellent co-operation of the contributors and the publisher, has this volume been made possible

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CHAPTER V

by J Grafton Love, M.D

CHAPTER VI

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by Bronson S Ray, M.D

CHAPTER VIII

by Olof H Pearson M.D

INTRODUCTION

Wilder G Penfield: A Brief Biographical Sketch*

Ira J Jackson, M.D

Doctor Penfield is a man of many facets. To the reader of this book an enumeration of his medical accomplishments would be redundant and therefore is omitted.

He was born in 1891, at Spokane, Washington, though since 1934 has been a naturalized Canadian citizen. At Princeton University, he was an excellent student and a football star He started one of the first Wilson For President Clubs on the Princeton Campus. In 1914 and 1919, he was a Rhodes scholar and has received 3 degrees from Oxford University In terrupting his studies during the first World War, Doctor Penfield served in France the latter part of 1916 as a dresser and was wounded in 1917 while at sea aboard the S S Sussex During his recuperation in England, he had the good fortune to convalesce at the home of Sir William and Lady Osler The association with Sir William Osler exerted a great influence on our guest in the years that followed. After graduating from Johns Hopkins Medical School in 1918 and spending several years in postgraduate study in Europe he became associated with Columbia University and Presbyterian Hospital in New York. In 1928 he was selected to head the Department of Neurology and Neurosurgery at McGill University in Montreal When the Rockefeller Foundation donated a million and a quarter dollars to McGill University to establish a Neurological Center to be second to none on this continent it was understood that Doctor Penfield would be at its head

He enjoys membership in many societies—both on this continent and abroad He is a Fellow of the Royal Society of London the Royal College of Surgeons, the Royal College of Physicians and the Royal Society of Medicine He is also an Honorary Fellow of Merton College at Oxford

Since 1939 he has received fourteen honorary degrees and has been specially honored by having received the Order of Saint Michael and Saint George in 1943 the United States Medal of Freedom With Silver Palms in 1948 the Chevalier of Legion of Honor in 1950, and in 1953 the pinnacle of awards the Order of Merit conferred by Queen Elizabeth II The Order of Merit is the highest honor that the Queen can confer upon her Common

* This is a revised version of the introduction by Dr Ira Jackson given Doctor Penfield to The Congress of Neurological Surgeons and their guests on November 1 1956

wealth subjects and is limited to only 24 members In 1954 he was elected to membership in the Athenaeum Club in London, which is reserved exclusively for men of great accomplishments in the Arts and Science.

Turning to the literary field in 1954, Doctor Penfield wrote "No Other Gods," a fictionalized version of Abraham's search for a monotheistic religion and his leadership of the Hebrew people on the journey to Canaan and a new destiny When Doctor Penfield visited his mother in Los Angeles in 1935, she had completed a novel on the life of Sarah, wife of Abraham, leader of the Hebrew people Since she appeared somewhat dissatisfied with her work he offered to take the manuscript with him and join her in authorship However, she died a few months later Nothing was done to this manuscript for the following 8 years. In 1943, during the War, Doctor Penfield was in Mesopotamia and read in a private library at Teheran an account of the excavation of Ur Ten days later he crossed the desert to Ur and 11 years later completed his novel "No Other Gods" He twice visited the site of ancient Ur while writing his book and brought to the recreation of those ancient days the scientist's thoroughness At present time he is writing a novel about Hippocrates and, with his usual thoroughness, he has visited the islands of Greece to obtain first hand information.

He heads the Montreal Neurological Institute as a father, watching and guiding his large international family Both he and Mrs. Penfield gave each new Fellow, no matter what part of the world he came from a feeling of belonging. They shared Sundays and holidays—especially Christmas—with the Fellows in the Penfield home, along with their own children.

In conclusion it is apropos to quote the president of Princeton in conferring on him an honorary degree—"A strong and gentle man with extraordinary dexterity"

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CHAPTER I

From Hippocratic Facts to Fiction

Hippocratic Foreword

WILDER PENFIELD, M.D

When I was a surgical interne in Boston, at the Peter Bent Brigham Hospital, I found that I was to have a little free time during one quarter of the service. So I approached the Chief of the Urological Service, William Quinby 'Have you some small problem you would like me to investigate?" I asked him. "I have a little free time coming."

He called me into his study "Before you begin any piece of research," he said "make a preliminary study Learn all that is known about the subject regardless of what language it is written in." He gave me Nagel's ponderous volume on the physiology of the ureter full of dreadful unending German sentences, each of them bristling with verbs at the end like the tail of a porcupine.

The preliminary took longer than the experiments which were carried out on rabbits at night After a proper period of gestation a little publication appeared on Contraction Waves in the Normal and Hydronephrotic Ureter The work was great fun and it almost made a urologist of me!

Again I saw the opportunity for a little free time, in November 1953 I could begin to take longer holidays with a clear conscience Free time! It comes to a physician like golden sunshine through a crack in the door, and with it should come fresh air and excitement.

I decided I would enquire into the beginnings of Medicine Was it possible I wondered to find out a little more about Hippocrates? We all know something about his teaching and his ideals We call him the Father of Modern Medicine How strange to know nothing about him or his life!

Every physician carries in his mind some sort of picture of the heroes of medicine You neurosurgeons know Ambroise Paré John Hunter, and William Harvey in medicine You know Osler, the warm hearted medical scholar the good physician. You know Cushing well, the man of many talents and many moods who made the surgery of the brain safe and reputable But I dare say you know nothing about the man, Hippocrates.

I decided to learn something about the influence that made him what he was But since there is no medical literature before Hippocrates, I found myself committed to a study of the life and thinking of Classical Greece as well as of modern Archeology—no small task for the vacation time of a mere surgeon!

It is that preliminary study I shall talk about this morning.

FACTS TO FICTION

WILDER PENFIELD, M.D

The beginnings of Modern Medicine are to be found in the Writings of Hippocrates They were collected, copied by hand and used as text books by physicians They were edited first in the tenth century after Christ and were translated and dissected in the Ninteenth and Twentieth Centuries. Many books make up the body of writings, the Corpus Hippocraticum. Since none was signed we cannot now decide what was written by Hippocrates and what may have been written by his teachers, pupils or associates, and how much was added by later coypists.

But through these writings there shines the light of unmistakable genius It seems altogether reasonable to conclude that this light comes from the thinking of one man, and that his name was Hippocrates.

He was born in 460 B C and died about 377 when Plato was 50 years of age and Aristotle was age 7, Socrates had been dead then for 22 years. All of these great men referred to Hippocrates of Cos of the family of the Asclepiads who trained men, for a fee, to be physicians Aristotle, writing some years after Hippocrates death, used him as example of the great physician (in his Politics VII, 4) and he did so in a way that shows how well he was known to Greeks in general

"Hippocrates," he said 'would be called greater not as a man, but as a physician than a man who is superior to him in stature.'

Aside from such oblique references there is little reliable information about his life There is the legend that he and the physician Euryphon from Cnidus, were called to treat the King of Macedonia and that Hippocrates refused a similar invitation to the court of the King of Persia in spite of the promise of great wealth. There lingers the scandalous rumor that he burned the medical library of a rival medical school Appearing in another form this ancient gossip suggests that he burned the temple of Aesculapius on the Island of Cos, a preposterous accusation especially since we now know the temple was built after he left the Island.

Other great men of Classical Greece are better known and these philosophers poets dramatists artists mathematicians still live today and move in the minds of many scholars. We marvel at the miracle of Greek mind and Greek culture for it lives today in our own minds and culture But Greek cities are gone and some are lost. Forlorn pillars still stand or have been set up again in Athens Delphi Epidaurus Mycenae Olympia Troy has been brought to light by digging down into the hill that guarded the entrance to their Hellespont our Dardenelles But the cities of the south eastern Aegean where modern medicine was born still wait for the spade of the excavator

In the Fifth century before Christ the seaport cities that lined the shores of the Aegean were Greek. They were proud, independent cities bound to each other by ties of culture and by friendly rivalries of athletics and intellectual exercise. But, in the latter part of the Fifth Century, fear of conquest by the rising power of Persia had made men look to the defenses of these cities. Persia, at least, had learned from a nation of sailors, the Phoenicians, how to conquer by sea as well as by land Thus made Persia a sudden threat to all the seaport cities of the Aegean The Aegean Sea is the body of water between the peninsula of Greece proper and the mainland of Asia Minor then called Caria Beyond Caria was the mighty kingdom of Persia

The result was that Athens had to build the great wall for her protection and many seaport cities farther east actually migrated to defensible position, building new harbors that could be defended They sometimes took their old names with them The fact that the dates of migration often are not known explains the archeological confusions to which I shall refer

With Mrs Penfield, I have made two voyages of exploration searching for clues to the life of Hippocrates, first in 1954 and secondly in 1956

In the autumn of 1954 we visited Greece and Turkey and since I had accepted the conclusions of the medical historians (1) at that time, we examined and photographed the west end of the Island of Cos where, it was thought, Hippocrates must have lived We did the same for the supposed site of the rival medical school of Cnidus, chartering for the purpose a Turkish caique, a sailing vessel equipped with auxiliary engine Thus, we explored the ruins of Cnidus the city having been excavated by Newton a hundred years ago but deserted since that time* (2)

After our return to Athens, and as the result of many discussions and much added reading we concluded that we were probably wrong in both instances First of all the capital of Cos had already been moved from the west to the defensible eastern end of the Island when Hippocrates lived there and second the city of Cnidus had not made its move to Tekir point until after that time!†

* The city is behind a great hill of rock called Cape Krio or the Triopium promontory It forms the tip of a peninsula on the southern shore of Asia Minor The peninsula is called the "Dorian promontory or Ancient Triopium" on the British Admiralty Map The tip of the peninsula is called Tekir by the Turks.

† Most important were the discussions with Luciano Laurenzi in Rome B D Meritt in Princeton and G E Bean in Istanbul. A long discussion with Henry Sigerist (3) whom we finally met in Rome was most helpful as was the correspondence with J M Cook, formerly Director of the British School in Athens and now in Bristol. This was supplemented by the opportunity to read in the London Library the Library of Princeton University and the Library of the American School of Classical Studies in Athens.

The little Island of Cos is close to the southern corner of Asia Minor It has boasted for 25 centuries that Hippocrates was born there.* Today the Coan citizens point with pride to a plane tree (Fig. I–1) near the harbor at the eastern end of the Island. Hippocrates, they say, once taught his disciples beneath its branches We differed with them in 1954. But, on our return to the Island in the spring of 1956, we could agree with them that it was possible How often ancient and unlikely tradition is found to have some truth in it! It is certain that the tree has been tended through many centuries by Greek and Turk and Greek again. Its mighty limbs are supported by marble pillars while new shoots grow up with strength from its roots

The most important evidence, in favor of the opinion that the major city in the time of Hippocrates was already in its present position came to light when a destructive earthquake occurred in 1933 The city was nearly destroyed at that time and in the debris was found a fragment of marble, bearing the fifth century Athenian law on currency It had been thrown down from the wall of a house where it had long been hidden from sight. This seems to indicate that the city located there, called Cos Meropis, was considered by Athens to be the capital of the Island in 449 B C when Hippocrates was a boy †

The rival school of medicine was located at Cnidus, not far away It seems likely that some of the books of the Corpus Hippocraticum were written by physicians from this city which was even more celebrated for medical teaching than Cos until the rise of Hippocrates

Like Cos, Cnidus also changed its site, because of the Persian menace, no doubt But the date of the move to the second site has never been certain. The Cnidian peninsula which was referred to as Cnidia or Triopia is a narrow ridge of bare mountains extending from the mainland of Turkey out into the Aegean toward Cos. Only at two or three points are there fertile

* It was because of the fame he brought to the Island that the splendid temple of Aesculapius was built there in the sacred cypress grove a short walk from the eastern harbor It was because of that medical tradition that Pharoah the first Ptolemy brought his wife there to be under the care of Coan physicians and thus Ptolemy II was born there

† This evidence is discussed by Meritt and his associates (4) The marble comes from the Pentelic quarries of Athens and the script is Athenian. It was a statement of the tax due from Cos as a member of the Delian League and it was apparently the intention of Athens that the marble should be placed in the market place It seems very unlikely that such a heavy marble would have been transported for building purposes from Astypalaia on the Bay of Camara at the other end of the island to Cos Meropis a distance of 25 miles. The earthquake occurred during the short period of Italian occupation of the Island. Extensive archeological studies were carried out at that time under the direction of Laurenzi (5) (see also Segre 6) and the damage was restored admirably by authority of the Mussolini government.



Fig I–1 The Hippocratic plane tree Island of Cos A group of German tourists sit beneath the tree while one of their number lectures to them on Hippocrates.

valleys which support the total 6,000 present day Turkish inhabitants, though scantily Wealth came from the sea in those early days and Cnidus II could seat more than that number in the smaller of its two outdoor theaters where Greek drama was played.

The peninsula is so narrow at the base, that it is almost an island and indeed the Cnidians once started to dig a canal at that point to defend themselves against Persia. That would have converted it into an island but the work was never completed Instead they moved the city from the south shore of the peninsula to its tip where they had two harbors, magnificently defensible behind a towering island of rock as mentioned above Cnidus II was certainly at that site after the time of Hippocrates and in later Hellenistic times

The first Greek historian, Herodotus was still a young man in his twenties living in the city of Halicarnassus when Hippocrates was born From that city he could see the white buildings of the harbor of Cos Meropis 12 miles away across the water From early times these three cities—Halicarnassus Cos and Cnidus—with three others on the Island of Rhodes—were joined together by a league that was as much religious as it was political called the Doric Hexapolis (Doric because they were settled by Doric Greeks from the Peloponnesus) For many centuries they sent their athletes every year to compete in the annual Festival of the Triopian

Apollo Almost the only record of the history of these cities has to do with this competition and with the successes of their athletes at Olympia, Delphi and in other pan Hellenic games

It is unfortunate that during the middle ages the crusaders used these islands and cities as bases of their campaigns against the so called "infidel in the Holy Land. The Christian knights destroyed with ruthless hands any beautiful Greek and Roman buildings that had escaped the recurring earthquakes At Halicarnassus they used for their fortress the marble from the tomb of Mausolus, called the mausoleum. It had once been one of the seven wonders of the world At Cos the walls of the knights castle contain lovely carvings from the temple of Aphrodite used as common building stones.

Fortunately Herodotus gave us a description of the Cnidian Peninsula as it was in the years when he (and also Hippocrates) knew it Recently two English archeologists Bean and Cook (7) recognized that this description did not fit the location of Cnidus and Triopion at Cape Krio or Tekir Point Consequently they made a survey of the peninsula examining the fragments of surface pottery They demonstrated that, during Hippocrates lifetime and on into the Fourth Century, Cnidus must have been located farther east at the site of the present village of Datça Triopion, where the games were held, they argued was at the site of another tiny village called Kumyer

On our second visit to Turkey we explored the length of the peninsula approaching it, this time by car from the State Capital of Mugla thanks to the Governor of that State and the courtesy of the Turkish government. We passed along hair raising roads that wound over the mountain sides and so came to the village of Datça where we accepted generous hospitality in the home of Mr Ziya Ekinçioglu, the local governor or *Kaymakam*

The first city of Cnidus was located on the seashore in this small but fertile valley The ground is covered with sherds or pottery fragments of the classical patterns. Evidently the migration of the city west to Tekir Point did not take place until well after the time of Hippocrates. The analysis of the surface pottery of the two sites carried out by Professor Cook seems quite adequate to prove this. And the descriptions of Herodotus fits that interpretation as we can testify

In the second fertile area of the peninsula a hill rises in a commanding position above the village of Kumyer two mile perhaps from the sand circled Bay of Palamut. A thousand meters off shore is the island called Baba Ada To this it would seem that a sea wall must have been built which made it a safe harbor for all the ships of the cities of the Hexapolis.

This statement requires verification from others Fortunately we entered the bay in a caique provided for us by the Kaymakam while he drove his

"jeep" (the only motor on the peninsula) from Datça to Cumali, so as to take us back in the evening. I noted that the bay would be an impossible harbor in a southerly wind and that there was only one position where a sea wall, or mole, would convert the island into a suitable harbor

On landing we inquired of the custom officer, who entertained us with coffee He made the statement that there was a wall below the surface of the sea running from shore to island at exactly that point. He apparently spends most of his time fishing and his lines, he said, regularly caught bottom there although there was deep water on either side Also, he had often seen the wall with his glass-bottom fishing box

Passing over the position back and forth in the Kaymakam's caique, I was able to see bottom, in the line of the supposed wall, at a depth of 1 to 3 fathoms several hundred yards out from shore and the same distance out from the island. On the other hand, the soundings shown on the British Admiralty map gave the depths of 14 and 31 fathoms there

On the towering hill above Kumyer, the Triopian Temple of Apollo might well have stood but this must be proven by excavation. We found the hill very rich in sherds of the same type as those found at Datça. The sloping hillside and level plane below would have made an ideal stadion for the sports in honor of Apollo

The conclusions of Bean and Cook (7) must be accepted, it seems to us. Our approval carries no more weight than that of any amateur But it seems clear that we are the first amateurs or professionals to explore this peninsula with an interest in the matter since the publication of their study in 1952 We may even take satisfaction in the fact that our report of a submerged sea wall at Palamut Bay adds real support to the contention of Bean and Cook that Triopion was in the valley at Kumver and that the games were held there both before and after the migration of Cnidus

So I came to the end of my preliminary study There is always a time when you stop perhaps in despair It is not that you have learned all there is to learn. But you conclude that you have a fair sample of what could be learned

On leaving the Cnidian peninsula, we rested then for a delightful period at the Hotel des Roses on the Island of Rhodes This gave us time to reconsider

After all, these questions of geography are not of primary importance, but it is necesary to deal with them as a preliminary To be understood a man should be seen in his own environment After he is gone the environment is all that is left to investigate.

I choose now to believe that Hippocrates as a young man lived next to the harbor at Cos Meropis He probably taught beneath a plane tree on the shore of the sea The rival school of medical teaching in Cnidus was

situated at Datça, 25 miles by boat across the blue water of the Aegean. The great festival of Triopian Apollo was celebrated each year in the lovely valley at Kumyer, 3 or 4 hours' walk from Cnidus

Many other things that *cannot be drawn on a map were part of his* environment. I've experienced some of them I've seen the sky and the water, the birds, the trees the flowers that Hippocrates saw I've smelled the air and felt the wind that he felt. I've read his writings and studied the lives of men he might have met. All this is written into my card index and lives in my memory These things add to environment or background.

Shall I turn away in disappointment now that I can find no more? Or shall I try to discover the man, presenting a picture based on hypothesis? I asked myself these questions while at Rhodes and one day I wrote out a message from the god of Medicine Don t think that I am a spiritualist. Take it as an allegory If I were living in olden times I would begin by telling you that I had a dreamed a dream. And in that dream I heard the voice of a man who cried out to me saying

'Let me speak! Let me speak! I am the God of Medicine, Asclepius the Greek god of Healing. After the Greeks the Romans called me Aesculapius. Hundreds of temples were built to do me honor and thousands of men found comfort and cure in them.

'You have forgotten the gods of Mount Olympus, you modern men. You think of us as myths and fancies of the people of the past. Those people knew that the many gods wore masks, and through those masks they could see the eyes of the living God

'You medical men pay me tribute still in every land on earth for you have taken my staff and the serpent coiled about it as a symbol of the best in your profession of medicine. Because of your tribute I will help you if you will but listen to me

"I can tell you much about Hippocrates. He is my own descendant, for I was not always a god First, I was a man I practiced medicine in Thessaly ten-days journey on foot north of Athens That was in the days when the Greeks were storming the walls of Troy and my two sons Podalirius and Machaon sailed to join the siege In the writings of Homer you may read how well they served King Agamemnon They were cunning leeches as well as warriors They pulled out Trojan arrows and spread on the soothing simples I had given them.

After Troy fell and the Greeks sailed home again in troubled triumph my sons returned to practice the healing art Podalirius excelled in the use of medicine and Machaon in surgery but they taught the whole art as Chiron had taught it to me They taught it to their sons and those sons to their sons generation after generation

These my descendants were called by the Greeks Asclepiads There

were many of them on the shores of Asia, especially at Syrna and Cnidus. But the greatest of the Asclepiads was Hippocrates He wrote down the medical secrets of our family, adding much wisdom of his own, so that medical men might know these things for all time and for all people He separated the true from the false, the proven fact from unprovable hypothesis. That was the beginning of medical science as you know it today

"Some centuries after my death, but long before Hippocrates was born, Zeus raised me up and made me an immortal god, the Greek god of medicine The Greeks, you know, had a way of telling and re-telling the stories of their heroes until they became great. They called me the blameless physician of Thessaly and told stories of me that were no more than fancy With their help Zeus created immortal children for me They symbolized the good things in medicine—two daughters Hygeia and Panacea and a son, the genius of healing, Telesphore

'Hippocrates was born in the Island of Cos in the year that the great Pericles came to power in Athens He lived through the golden age of Hellas. And he is still my chief source of pride although there were in those days other good Asclepiads practicing in Cos and in Cnidus

You have learned a little about the way of life in the Greece of that day You have lived where he lived and read what he wrote You have read the scandals the falsehoods men told of him, saying he burned the library of medical manuscripts in Cnidus from jealousy

'But don t turn away because you have discovered so little Study the problem with reverence, for he is your first medical hero Men live by their heroes

The voice was silent and I feared that Asclepius was gone so I called out to him. But the voice began again. It seemed to be at my elbow now

'Listen to me! Paint a picture for yourself dipping your brush in the colors of fancy There will be errors in the minor detail But you may make fiction tell a truth to which history is blind After all fiction is the stuff that clothes all heroes and I will guide your hand.

Take for the time of your tale a few months in the year when Hippocrates was 28 You would call that year 432 B C Take that as the year in which the library at Cnidus was burned The burning occurred just after the festival of Apollo at Triopion It was a woman who burned it. She set the stage so that men should blame Hippocrates. Say that her name was Olympias and that her son loved Daphne, the daughter of Euryphon, the great physician of Cnidus Hippocrates loved Daphne also Through romance and tragedy temptations and successes Hippocrates continued with single purpose You know now his way of healing teaching studying.

Begin the story as though you were embarking on a project in medical research Observe the laws of nature, the law of cause and effect Men s

reactions have not changed any more than diseases have. Write as well as you can Be simple and clear Recognize the beauty in life as well as its ugliness

"Start on the work, though you cannot see the outcome No man should hope for inspiration until he has earned it by his labor That is as true of writing as it is of research Inspiration comes to the man who works with an open mind, the man who waits for wisdom"

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CHAPTER II

Thoughts on the Function of the Temporal Cortex

WILDER PENFIELD, M.D

Some people say that the heart is the organ with which we think and that it feels pain and anxiety ' But I hold, "That to consciousness the brain is messenger For when a man draws breath into himself, the air leaves in the brain its quintessence and all that it has of intelligence and sense '

"Men ought to know that from the brain, and from the brain only, arise our pleasures joys, laughter and jests as well as our sorrows, pains, griefs and tears. Through it in particular, we think, see, hear, and distinguish the ugly from the beautiful, the bad from the good, the pleasant from the unpleasant."

Those words were written by Hippocrates 2500 years ago and it is significant that they were found in a book on epilepsy which was called "The Divine Disease '

It is of course, as easy to say that men think with the brain as it was to say that they thought with the heart or the liver

How is the brain used? That is the question today What subdivisions of function are there within the brain? How do the parts work? What integrates their action?

It was a surgeon who started off the work in cerebral localization. Paul Broca pointed to what he called the seat of the faculty of articulate language in 1861 A physician Hughlings Jackson, became the prophet of the gospel of functional localization within the brain He had a guide to the working of the brain the same guide that Hippocrates must have used He saw in the patterns of epileptic seizures a mapping of the functional areas The serial representation in the cerebral cortex, of the crude movements of the different parts of the body and crude sensation of those parts as well were clear almost at once

He saw in what he called the dreamy states, clues to the nature of the higher intellectual functions These are the functions that we must discuss in any consideration of the temporal lobe He referred to them as—"Psychical states during the onset of epileptic seizures states which are much more elaborate than crude sensations I speak first ' he continued "of certain highly elaborate mental states sometimes called intellectual aura ' I admit the term intellectual aura is not a good one The state is like that occasionally experienced by healthy people as a feeling of 'reminis

During an experiential hallucination a patient may hear music, for example. But if so, he hears a single playing of the music—orchestra, piano, or voices—and he may be aware of himself as present in the room or hall. He may hear voices, the voices of friends or of strangers. If they seemed familiar to him during the interval of time now being recalled, they are familiar to him now. If they were strange then, they are strange now. He may see the people who were speaking and the piano being played, with the man who played it. He may on the other hand see things that he saw in an earlier period without being aware of sound. If he felt fright then, he feels fright now. If he felt a pleasurable admiration then, he feels it now.

It is a re-creation of those things on which he was focusing his attention in that interval of past time. Now, however, he is conscious of the present as well as the past. It is a little like the double experience of a man who watches a play and yet is conscious of what is going on about him in the audience. The difference is that he discovers himself on the stage of the past as well as in the audience of the present.

When such an experience constitutes the beginning of a seizure, we have called it a psychical hallucination. It is clearer to call it an experiential seizure. During that and during an experiential hallucination produced by electrical stimulation, there comes back into his present consciousness an awareness of the stream of experience that passed through consciousness in that earlier period.

There is then stored away in the ganglionic connections of the brain a permanent record of the stream of consciousness. A record that is much more complete and detailed than the memories that any man can recall by voluntary effort.

I made a map of the areas of brain from which stimulation had produced such experiential hallucinations (9). The area that is stippled in Figure II–1 was that from which stimulation sometimes brought back a vivid strip of past experience. But it is also within this general area that perceptual illusions are produced and it might be worth while to reconsider what these things, in terms of normal function, may mean.

Dr. John Mullan* and I have made a study of the perceptual illusions among recent cases of temporal lobe seizures.† All patients in the series had electrical stimulation of the temporal lobe during operation. The stimulation was carried out as an aid in planning the therapeutic excision of cortex. Mullan reviewed 214 consecutive cases to which 3 earlier examples were added because of special interest. In this group of 217 patients,

* Formerly my associate in Montreal but now a member of the Neurosurgical Department of the University of Chicago.

† This study will be reported in detail at the meeting of the American Neurological Association in June 1957. It is reported here in preliminary form only.

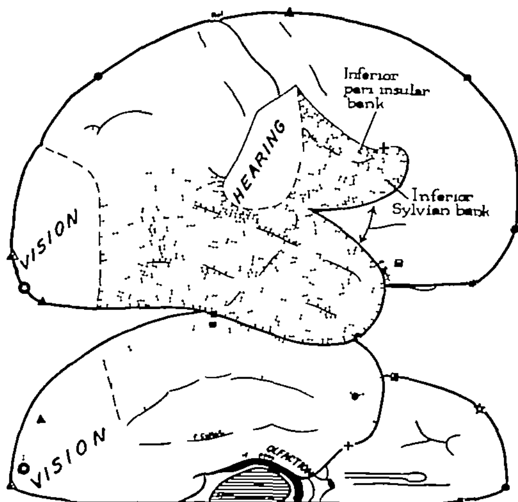


FIG II-1 Physical responses, stippled. The superior surface of the temporal lobe is turned upward The boundary of this cortex, from which stimulation has produced psychical illusions and evoked recollections, is not quite certain in the parietal and inferior temporal regions (3)

73 had experienced perceptual illusions as an aura before operation or they had such illusions produced by stimulation. In many cases they had both Most of the perceptional illusions may be easily examined under the headings shown in Figure II-2

The auditory illusions of change in loudness distance or tempo of sounds were produced by stimulation in the temporal lobe of the minor or major hemisphere with equal frequence and the stimulation points were on the first temporal convolution or close to it. (Fig. II-3)

Visual illusions of alteration in clearness distance nearness shape speed of movement and erectness which occurred during epileptic discharge arose in the temporal lobe of the non-dominant—the minor hemisphere for handedness—in 10 out of 11 cases In this exception it was in the temporal cortex of the dominant hemisphere

PSYCHICAL ILLUSIONS

ALTERATIONS OF PRESENT INTERPRETATION

1 *Auditory illusions*
Distance Loudness Tempo
2 *Visual illusions*
Distance Dimension Erectness Tempo
3 *Illusions of comparison*
Familiarity Strangeness Unreality
4 *Illusional emotions*
Fear Loneliness Separation Sorrow Disgust

FIG. II-2. Interpretive illusions of present experience

On the other hand stimulation produced these illusions in the minor hemisphere for handedness only The points of stimulation were scattered over the lateral surface of that temporal lobe. (Fig. II-4)

We were surprised to discover that these illusions depended in such a large majority upon *the non-dominant hemisphere and therefore* we recalled 2 earlier cases in which we remembered that such illusions had been produced in the hemisphere dominant for speech In both cases, however, the hemisphere was found to be non-dominant for hand! This would suggest strongly that the interpretation of position and shape—as well as of clearness and speed of things—depends particularly upon the function of the temporal cortex of the hemisphere which controls the minor hand.

However this actually is in conformity with the findings of our associate Dr Brenda Milner (who will report in the next meeting of the Association

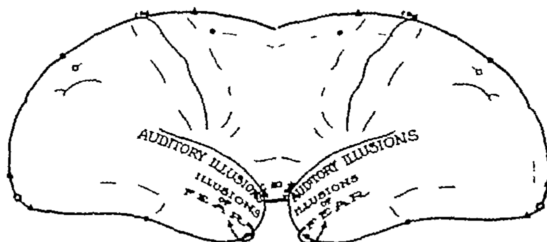


FIG II-3 Areas from which stimulation at operation produced (a) Auditory illusions—change in distinctness, loudness, character of things heard largely on first temporal convolution of either hemisphere (b) Illusions of fear—nameless fear fright, nervous feelings, largely from under surface of anterior temporal pole of either hemisphere

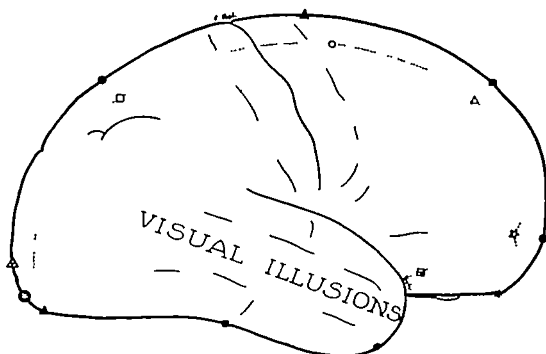


FIG II–4 Visual illusions. Area in which stimulation produced an illusion of change in position dimension rate of movement, distinctness of the things seen. In 12 different cases stimulation produced these illusions, but all were in the minor hemisphere although 40 per cent of the total operations were on the major hemisphere Among 11 patients who had such visual illusions at the beginning of attacks, the localization in 10 cases was in the minor temporal lobe for handedness and only one in the major hemisphere (See Penfield and Mullan, 1957)

for Research in Nervous and Mental Diseases) that psychological tests of patients after anterior temporal removal on the minor side show that they have some defect in the recognition of the significance of pictorial material. Anterior removals on the dominant side do not produce this defect but leave them with some difficulty in remembering stories expressed to them verbally, although they have no aphasia

Illusions of familiarity (déjà vu) were produced by stimulation only in cases in which this had been reported by the patient as an aura They also occurred predominantly as the result of discharge or stimulation in the temporal lobe of the hemisphere which was minor for speech and handedness (Fig. II–5)

Fear in different forms occurred frequently and we accepted it as an illusion of interpretation It was produced from one hemisphere as often as from the other The localization was usually in the anterior and inferior surface of one temporal lobe (Fig. II–3)

To summarize then illusions in regard to things heard and the feeling of fear are produced by discharge in the temporal cortex of both sides

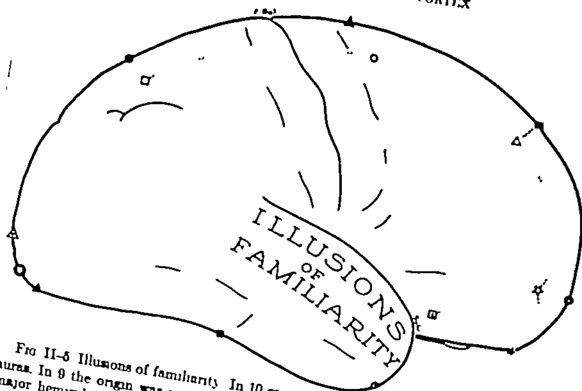


FIG II–5 Illusions of familiarity In 10 cases patients had such illusions as epileptic auras. In 9 the origin was minor temporal lobe and in one the temporal lobe of the major hemisphere Stimulation reproduced the illusion in 6 cases all on the minor side for speech and handedness. (Penfield and Mullan 1957)

equally The illusions of familiarity in regard to things seen arise most often from discharge in the temporal cortex of one side that of the minor hemisphere

DISCUSSION

It is obvious that a large portion of the cortex of the temporal lobes is somehow employed in the understanding of present experience and the re cording of that experience This is neuronal activity which is on a higher functional plane than that of motor or sensory areas of cortex. The motor and sensory areas seem to serve only as transmitting and perhaps trans muting stations for the motor outflow and the sensory inflow that connects the integrative circuits of the centrencephalic system with the body periphery

The evidence as to location of sensory areas in the human cortex as determined by stimulation is shown in Figure II–6 The motor areas of the cortex are summarized in Figure II–7

It may be said that the temporal cortex is devoted to the normal processes of perception But perception must be understood to mean something more than reception of sensory stimuli This perceptional cortex is involved with the centrencephalic system of the higher brain stem in the interpre

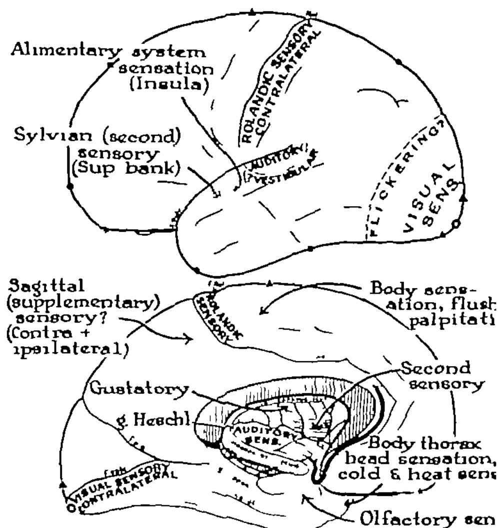


FIG II-6. Sensory areas of the human cortex as judged by stimulation explor in conscious patients. The insula, in which there is some sort of representation of alimentary tract has been removed in the lower drawing of the mesial surface of brain. The "body thorax head sensation cold and heat sensation" shown in the terior temporal pole calls for further verification. (Penfield and Mullan, 1957.)

tation of those things of which an individual is aware and the compari of the present with past experience

This conclusion follows because of the nature of the illusions produ by independent ganglionic discharge in that area. It is as though cert routine questions were asked of the temporal cortex at the time of e new experience and as though replies were returned through a limi number of standardized answering mechanisms.

The answers indicate whether this has been experienced before whet strange whether familiar whether fearful And other judgements expected concerning the individual s enviroment There must be a fi common path that leads back into the central integrating circuits

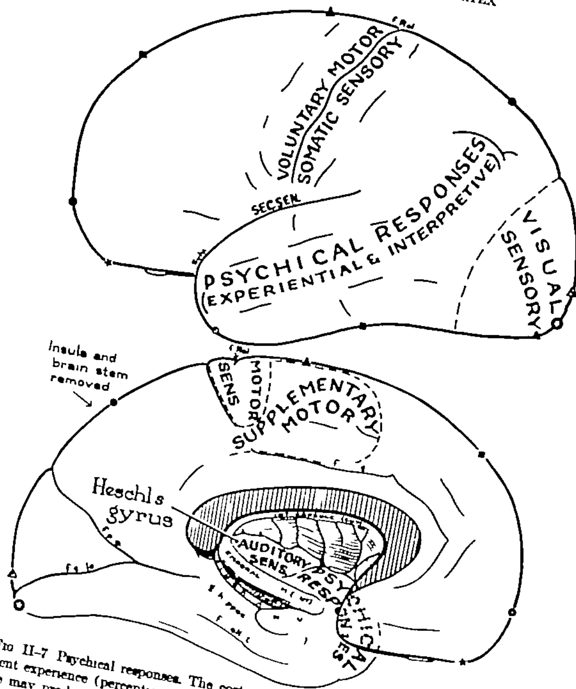


FIG II-7 Psychical responses. The cortex which is important in interpretation of present experience (perceptional cortex) is marked 'psychical responses. Stimulation there may produce interpretative illusions or experiential hallucinations. The insula has been removed in the lower drawing

Certain constantly recurring conclusions are thus handed on, such as 1) I have experienced this before " "it is familiar 2) 'There is danger " something to be afraid of 3) Things coming closer' or 'going away " 4) Dimensions changing.'

Before these final interpretations of present experience are possible it is obvious that the present must be compared with the past. In order to

carry out such a comparison the record of the past must somehow be made available

Take, for example, a simple experience You focus your attention on a man who is approaching—all the previous experiences in which that man *was the center of your attention are summoned and reviewed* with no voluntary effort on your part The smile and the gesture of the hand in greeting are familiar, but he is limping—that is strange Gray hair at the temple that is new He speaks, the voice is familiar There is a gun in his other hand, pointed at you. You feel the signal of fear, a secondary sensation in the epigastrium perhaps

Those same signals that may come to the consciousness of an epileptic *as illusions during a perceptual seizure are now serving their normal* useful purpose familiarity strangeness, familiarity, fear They are simple signals to consciousness derived now from the most complicated comparison of the present with many past experiences. All these signals are sounded without conscious effort to recall memory Even the name of the man is suddenly provided— John Jones,'—the bad man of past acquaintance

The area of cortex which 'turns in' these alarms or signals must of *necessity also be closely connected with the recordings of past experience* and so it is not surprising to discover that the other phenomenon produced by local independent neuronal activity in this area of cortex is the recall of strips of past experience You had compared the man approaching you with John Jones as he appeared in earlier meetings—walking toward you or away, waving smiling or speaking—perhaps many years earlier And you called on other strips of experience in which guns were pointed and danger signalled

Once some days afterward a patient questioned me about her operation 'You forced me she said to live again things I had forgotten What were you doing? Were you stimulating my subconscious mind?' I laughed at her naive question And then I stopped to wonder Wasn t that exactly what my electrode had done?

Yes in a sense she was right. The identification of John Jones as he approaches is carried out by the subconscious processes of memory The perception and recognition is all done for you before your conscious command of memory takes over Then you recall something about the man but your conscious memory of him is a sort of generalization of the many meetings and the things you have heard of him.

Having focused your attention on him you begin to record this meeting and because of the fear of the gun perhaps that record will remain indelibly available to conscious recall as well as for the subconscious purpose of comparison.

Our new evidence suggests that when you are laying down the record of

your meeting with "John Jones" you are using the amygdaloid nuclei and the hippocampal complex of the two temporal lobes The complete integration of the experience can only be carried out by combined action of the sensory systems with the coordinating centrencephalic system, much of which must be in the brain stem It would seem, however, that the comparison of the present with the past is a function of the temporal cortex

CONCLUSION

In conclusion, it may be said that the temporal cortex, especially that of the superior and lateral surfaces of each temporal lobe, is devoted to perception. (see the area of psychical responses, Figure II-7) It provides certain interpretations of present experiences—interpretations that are curiously standardized They make it possible for the conscious man to recognize any present experience as familiar, strange, fearful, nearer, farther, louder, fainter, disproportional, etc

A permanent record of present experience is only possible when the bilateral mechanism of the amygdala and hippocampal complex is functioning normally

It is certain that the past record is called upon subconsciously during the interpretation of present experience This is prerequisite to normal perception The record of the past may well consist in a facilitated pathway formed by the passage of nerve impulses through ganglion cells of the temporal lobe. These conclusions are rendered more probable by the fact that stimulation of the perceptional cortex may produce detailed recall of the past as well as illusion of interpretation of the present.

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Questions and Answers

QUESTION In psychic seizures, should the minor lobe always be resected? if so how much of the lobe should be resected?

DR. PENFIELD We use the word psychical seizures because Jackson did and seemed to take it out of the psychic research field—I take it that temporal lobe seizures is meant. I don t use the word psychomotor, either because one is not sure just what localization is meant. I like to be as anatomical as possible In temporal lobe seizures of course, the site of resection depends on where the fit is coming from Temporal lobe seizures are exactly like other focal seizures in that they are arising somewhere If the abnormality is all in one temporal lobe, you have a chance of having

reasonably good results, providing you remove the origin. There is no reason always to take the minor lobe rather than the major, except that on the major side you have a little more to pin it on

With respect to the extent of resection, usually there is a vein that indicates the frontier of removal Actually on either major or minor side, you can remove about 5 cm, measured back from the tip Coming down to the medial surface you take the hippocampal formation back to the end of the hippocampus. That is the only difficult part of the operation, but it is really quite simple if you stay inside the reflection of the pia as it runs upon the midbrain In my opinion, no surgery on the temporal lobe for seizures will ever be satisfactory or successful unless this zone is removed. If you have a bilateral focus—that is, if the seizure is coming from both temporal lobes—then there is danger in the bilateral removal of the hippocampal gyrus. You may interfere with memory, as I mentioned in my talk. You will *not get aphasia on the dominant side if the removal is restricted to the* anterior 5 cm of the temporal lobe

QUESTION Can you tell the obstetricians anything about the prevention of epilepsy since you think that most of the temporal lobe injuries are at birth

DR. PENFIELD Yes, I can tell them, but I don't think they will listen. A very short time ago we began to realize that temporal lobe epilepsies are caused by an obstetrical lesion, and no obstetrical clinic as far as I know has taken an interest in it In looking at the shape of the infant's brain and the shape of the incisura of the tentorium, I would assume that bilateral pressure from side would tend to keep the incisura closed and not promote the herniation of the temporal lobe whereas pressure from the back would relax the tentorium and make herniation easier I think that this is something in which the obstetrician should begin to take an interest. The difficulty is that the temporal lobes are not used for the first year or two of life and there is no way to examining new born infants and saying this child has had decrease in circulation of the temporal lobe and in later life he is going to have temporal lobe seizures It is an obstetrical problem. How the thing is going to be studied and prevented I do not know

QUESTION Is there a specific area for cortical representation of the genitalia for instance sexual sensation or association?

DR. PENFIELD It's a curious fact that in my own experience I have found no evidence of any relationship of the cortex *to sexual activity The only* evidence of such is the patient reported by Ericson who had a neoplasm between the two hemispheres and who had seizures that seemed to involve great sexual excitement. In the cortex itself in my experience there is no representation or place for sexual sensation or activity

QUESTION Do you have physiological or anatomical data explaining the mechanism of ganglionic memory recordings?

DR. PENFIELD That is a very fundamental question. We don't know what the mechanism is for this record which we know is certainly there. There have been various suggestions, in my own opinion, I can only assume that the millions and millions of ganglion cells in the temporal areas, (each cell having anywhere from 500 to 700 collateral branches), there is a tremendous opportunity for patterning through those cells. With the progress of each conscious experience, there is a facilitated pathway through these ganglion cells which remains permanent. It is passed over only once with each experience, and the sequence of this pathway becomes permanent. I suppose it is from cell to cell across the connections of cells that this facilitation remains in a permanent basis, that must be the basis of memory There are many other forms of memory Once there has been a passage through a cortical system, there is a permanent lowering of threshold, somehow

QUESTION Will you comment on the question about visual and motor illusions experienced by patients during attacks of Meniere's Disease as related to the temporal lobe?

DR. PENFIELD I don't understand that question, but I suppose that certainly there are cases in which—during an illusion coming at the beginning of an attack—the patient has a change in the way he sees things. They are no longer erect, or they may be coming closer to him or going farther away, or they become lop-sided. This seems to be a function related to the non-dominant temporal cortex. Certainly all of those cases that we have been able to localize have been due to discharges in the non-dominant, that is the temporal lobe which is minor for hand. You see the same type of difficulty after all in the patient who has a lesion of the temperoparietal cortex in the non-dominant hemisphere after removal or after an injury there. The patient can no longer visualize the form of external objects and he cannot visualize his own relationship to them, so that he gets his clothing all mixed up, and he can't draw a picture of a square Those things certainly hang together

CHAPTER III

Ocular Manifestations of Pituitary Tumor

C WILBUR RUCKER, M.D

INTRODUCTION

It is appropriate that an ophthalmologist should present the first paper in this symposium on pituitary tumors as a large proportion of patients who have pituitary tumors complain first of disturbance of vision. An alert ophthalmologist, when he cannot readily explain a reduction of acuity by the patient's refractive error or by ophthalmoscopic examination charts the visual fields. It is to the discredit of ophthalmology that some patients with pituitary tumors have had several changes of glasses before their oculists have charted their visual fields and localized the source of their difficulty A few patients, on the erroneous diagnosis of chronic retrobul bar neuritis have even received fever therapy or large doses of vitamins or cortisone The ophthalmologist, alone cannot make the diagnosis of pitui tary tumor but he can find evidence of involvement of the optic chiasm, and even determine where and how extensively it may be involved. After roentgen ray or surgical treatment of the tumor the ophthalmologist can report on the immediate and later visual changes, whether they are in the direction of restitution or of further loss Since it is largely for preservation of vision that surgical treatment is performed, the ophthalmologist's role is vital, both in diagnosis and in long term follow up

DEFECTS IN THE VISUAL FIELDS

The course of the fibers through the optic chiasm is indicated in Plate I It should be pointed out that the drawings are based on studies made 30 years ago by Wilbrand that some of the details are unconfirmed, and that consequently there may be minor inaccuracies. The drawings are acceptable as a working basis however the reader must bear in mind that they represent the current concept of the chiasm and that they are subject to change in the future as more precise knowledge b[illegible]mes available

According to Wilbrand (7 8) the c earest picture of the chiasm is obtained by thinking of it as composed of three layers In the upper layer are fibers from the upper quadrants of the retinas, non crossing fibers out

PLATE I COURSE OF FIBERS THROUGH THE OPTIC CHIASM (5)
(From Rucker by permission of the American Academy of Ophthalmology and Otolaryngology)

number the crossing fibers In the middle layer the crossing fibers are largely from the upper nasal quadrants of the retina, the non-crossing fibers largely from the lower temporal quadrants, the numbers of crossing and non-crossing fibers are about equal In the lower layer of the chiasm the crossing fibers arise in the lower nasal quadrant of the retina and loop forward into the optic nerve of the opposite side before they turn backward to enter the optic tract It is this bundle which is usually interrupted first by a pituitary tumor pushing against the lower and anterior portions of the chiasm. The relatively few non crossing fibers in the lower layer are from the lower temporal quadrants of the retinas

Kestenbaum (4) has clarified the complex relationships within the chiasm by the concept of a 45-degree rotation of the optic nerve around its longitudinal axis as it enters the chiasm. The upper part of the nerve rotates nasally, the lower part temporally There is a further 45-degree rotation in the same direction in the optic tract This leads to the upper quadrants of the retinas being projected onto the nasal portion of the lateral geniculate body and the lower quadrants onto the temporal portion. The projection of the horizontal midline of the retina stands vertically in the lateral geniculate body Counter rotation occurs in the beginning of the optic radiation where original relationships are resumed the upper quadrants of the retinas are projected superiorly, the lower quadrants are projected inferiorly

Pituitary tumors produce defects in the visual fields when they become large enough to press against the optic chiasm. The pressure and displacement obstruct the function of the nerve fibers Even more important, probably, is the interference with their blood supply The tumor obliterates the capillary bed at the site of pressure and, by pressing against small arteries and veins may occlude vessels in other portions of the chiasm and interrupt bundles of nerve fibers not directly involved by the tumor Large tumors may push the optic nerves and chiasm against firm neighboring structures, such as the edges of the optic canals or arteries of the anterior portion of the circle of Willis, and these in turn may interrupt more fibers than the tumor itself This is a late effect however The early disturbance in vision has reliable localizing value

For the demonstration of defects in the fields of vision a vast number of instruments have been designed over the years, and a wide variety is available today Some are merely fancy gadgets, some are research tools, some have special features of distinct but limited value, other relatively simple models are best suited to office use The ideal perimeter, to my mind, is not presently available since manufacturers find greater profit in elaborate equipment than they do in simple basic instruments

For exploration of the periphery of the field I prefer a perimeter with an

arc having a radius of 0.33 meter and painted dull black or covered with black felt. A 3-mm. white bead on the end of a black wand is a suitable target, larger white disks are employed as necessary for charting the density of defects.

For adequate exploration of the central area of the visual field the perimeter offers such a short working distance that the requisite test objects are too small for practical handling. A tangent screen serves this purpose, since it permits the meticulous examination of the field out to 30 degrees. A 1-mm. white bead should be visible over most of the screen at 1 meter except at the physiologic blind spot if there is no defect. Any defect discovered and charted with a small target is next explored with larger targets which may be beads or may be white disks fastened to the ends of dull black wands The largest target that can be made to disappear indicates the density of the defect.

The fields are recorded on charts that represent the field as the patient himself sees it. The field for the right eye is placed to the right on the chart, its upper portion above, its temporal portion to the right its nasal portion to the left. The test object used is recorded by a fraction the numerator indicating the size of the test object, the denominator the distance at which it was used For example 3/330 indicates that a 3 mm. bead was used on the arm of a perimeter which had an arc radius of 330 mm. Likewise 1/1,000 indicates that a 1-mm bead was used at the tangent screen at a distance of 1 meter The boundary of the field for a given target is known as the isopter for that target (5)

The characteristic change in the visual fields from a lesion at the optic chiasm is bitemporal hemianopsia the result of interruption of crossing fibers When the lesion is a chromophobe adenoma it may not necessarily grow upward in the midline. It may extend to one side or the other, forward or backward. In growing forward it may impinge on the optic nerves and produce scotomas or it may completely interrupt the optic nerve on one side before it grows across the midline to the other It may grow backward against one of the optic tracts and produce incongruous homonymous defects. When the tumor attains a large size it may press the chiasm or the optic nerves against rigid neighboring structures with resultant further visual loss.

An example of the ordinary bitemporal hemianopsia is furnished by the following

Case 1—A 47 year-old farmer complained of failing vision weakness and headache Vision had been impaired for 5 years and the patient him self had noticed that with each eye the loss was to the outer side Two years after the onset of the visual disturbance he lost most of his pubic hair and his friends told him he looked pale. His local physician assured him he

was not anemic and said his symptoms were most unusual, but did not suggest further consultation For 1 month prior to admission he had felt excessively weak, and for 3 weeks had suffered from numerous headaches, intense but of short duration.

Ophthalmoscopic examination disclosed moderate pallor of both optic disks Perimetric fields demonstrated complete bitemporal hemianopsia (Fig III–1), indicating interruption of all of the crossing fibers at the optic chiasm. Roentgenographic examination of the head showed the sella turcica to be greatly enlarged by an intrasellar tumor At general physical examination there was evidence of hypopituitarism A neurosurgeon, through right transfrontal craniotomy, encountered a huge chromophobe adenoma which had extended upward 6 cm. from the base of the sella

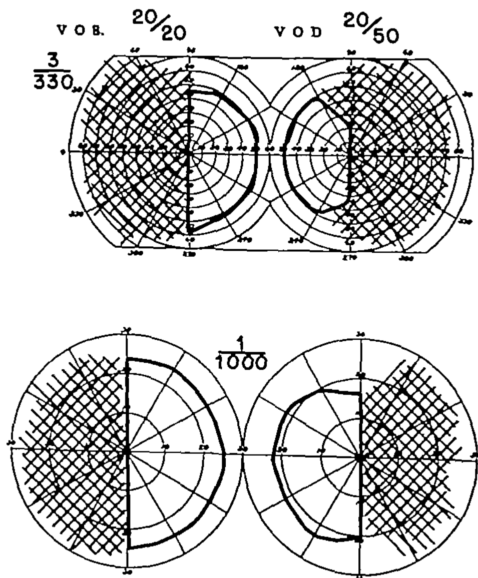


FIG. III–1 (case 1) Complete bitemporal hemianopsia

turcica and had displaced the optic nerves laterally and the chiasm posteriorly. He was able to remove the tumor and its capsule. There was no improvement of vision, and probably none was to be expected, for the optic nerve heads were atrophic at the time of operation.

The patient has returned at regular intervals during the past 10 years. At his last visit, about 1 year ago, he was taking desiccated thyroid, cortisone and testosterone. The optic disks were nearly white. The bitemporal hemianopsia has remained unchanged.

Minimal defects in the visual fields may be demonstrated at the tangent screen with small targets. In our experience, a 1 mm. bead at 1 meter is the smallest practical target for the average patient. Patients who are unusually alert may give reliable responses to the 1 mm. bead at 2 meters, but we have not found a target as small as that to be useful in everyday clinical work.

An example of a small defect in the fields follows.

Case 2—A 24 year old woman complained of a mild disturbance of vision first noticed 9 months previously. For 1 year she had been chronically fatigued and liked to have the temperature of her house about 80. For 2 weeks there had been frequent pains about the right eye. Her menstrual periods had begun at the age of 13 years and had ceased at the age of 20 years, 3 years before the onset of her visual complaint.

The ocular fundi appeared normal. Perimetric fields (Fig. III–2) showed a depression in the upper temporal quadrants, indicating a partial involvement of crossing fibers at the anterior margin of the chiasm. Roentgenograms of the skull showed decalcification in the dorsum sellae on the posterior clinoids and on the left anterior clinoid, characteristic of an intrasellar tumor. The neurosurgeon found and removed a cellular chromophobe adenoma, which presented under the chiasm and between the optic nerves. A week after operation visual fields were normal and remained so for the year the patient stayed under our care.

Occasionally the visual loss assumes the form of bitemporal scotomas. Since the fibers that arise in the central portion of the retina decussate largely in the posterior part of the chiasm, it might be inferred that bitemporal scotomas point to pressure at the posterior margin of the chiasm. This is true at times, but not invariably by any means. Bitemporal scotomas may be associated with relatively recent visual loss, most often less than several months. The reason for this is not clear.

Case 3—A 50-year-old housewife 6 months before admission had noted a vague blurring of vision and some black specks before her eyes, not of sufficient annoyance to warrant seeking medical attention. Three months previously she had begun to have intense headaches which wakened her at 4 a.m. with stabbing pain. Within an hour the pain would subside to be

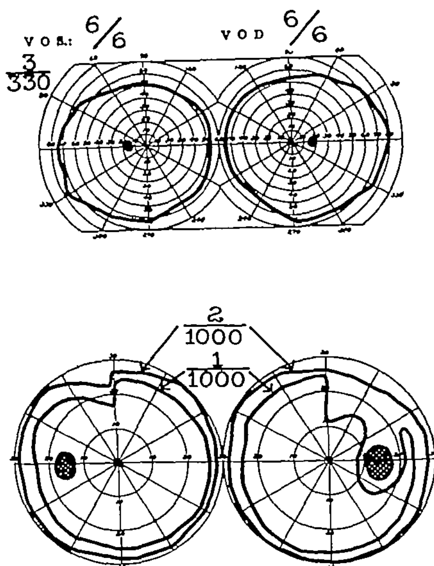


Fig III-3 (case 2) Partial bitemporal hemianopsia

followed by blurring of vision The optometrist she consulted referred her to an internist who treated her for anemia Because of continued loss of vision she consulted an ophthalmologist, who ordered roentgenograms of the skull and sent her to a clinic for neurosurgical consultation. On admission visual acuity was somewhat reduced, the ocular fundi appeared normal visual fields (Fig III-3) contained large, dense bitemporal scotomas Roentgenograms of the head showed enlargement of the sella turcica by intrasellar tumor The neurosurgeon advised and carried out an operation at which he found a large chromophobe adenoma anterior to the chiasm which had compressed both optic nerves and displaced the chiasm posteriorly He resected a large part of the tumor and its capsule. Ten days later the visual fields were almost normal

Since the optic nerve heads had good color and the visual loss was of

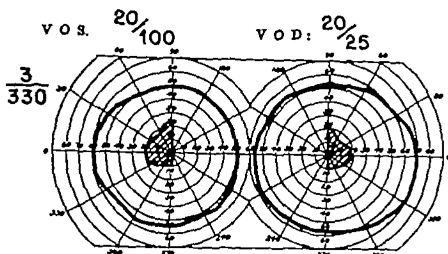


FIG. III-3 (case 3) Bitemporal scotomas

relatively short duration, this fortunate outcome was perhaps to be expected. In this case the bitemporal scotomas are apparently to be attributed, not to the precise location of the tumor, but to the recent involvement of the chiasm.

When the pressure of the tumor is against the optic nerves rather than the chiasm, either central or arcuate scotomas may arise

Case 4—A 24-year-old woman complained of headache and amenorrhea of 2 years' duration. Her menstrual periods had begun at the age of 15 years and had been regular until the age of 22 years when they ceased On examination of the eyes the fundi were normal and the perimetric fields full Roentgenographic examination of the head showed enlargement of the sella turcica with erosion by intrasellar neoplasm. The neurosurgeon advised deep roentgen therapy to the region of the pituitary body Three treatments were administered.

After 4 months she returned again. Frontal and occipital headaches had been constant since the previous visit She was depressed and had frequent crying spells. The optic nerve heads appeared normal Charting visual fields (Fig III-4) demonstrated in the field of the left eye an arcuate scotoma Roentgenographic examination of the head showed evidence of an intrasellar tumor eroding the sella turcica and its posterior clinoids. Because of the impairment of vision of the left eye the neurosurgeon advised and carried out a craniotomy, encountering a pituitary tumor projecting upward anterior to the chiasm and compressing the left optic nerve He removed all of the tumor that he could see On postoperative recheck the perimetrist found (Fig III-5) that the scotoma had increased in density and that there had been further visual loss in the nature of a bitemporal depression

Five years later the arcuate scotomas were so slight that they were

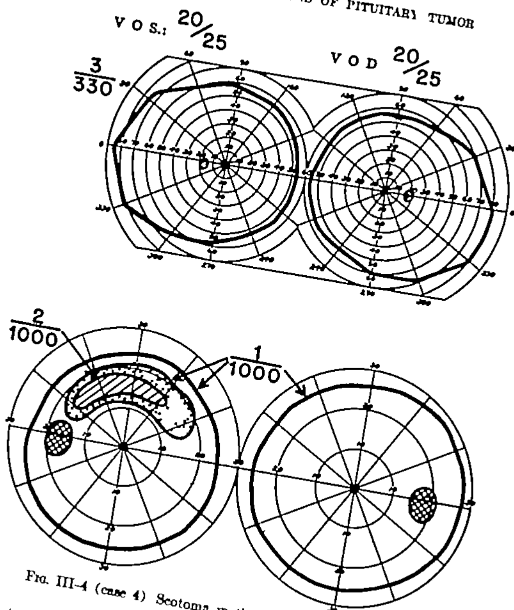


FIG. III–4 (case 4) Scotoma in the field of the left eye

demonstrated with difficulty (Fig III–6) In the interim the patient had been aware of improvement in vision, but continued to have daily headaches and was tired all the time, worried and easily upset

Central scotomas occur uncommonly as a consequence of pressure from pituitary tumor An example is furnished by the next case.

Case 5—An 11 year-old boy complained of polyuria and polydipsia, listlessness and occasional vomiting of 30 months duration. Pitressin, prescribed by his family physician had given some relief For 1 month prior to admission there had been pain in the right eye and over the right side of the head. On examination visual acuity and the ocular fundi were normal Roentgenographic examination of the head showed an irregularity of the floor of the sella turcica on the left side that was interpreted as a

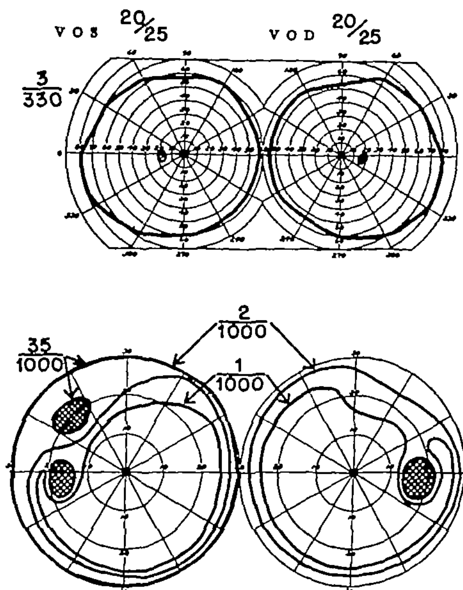


Fig III-5 (case 4) Bitemporal depression

developmental variation. It was suggested that roentgenograms be taken again in 6 months for comparison. The pediatrician made a diagnosis of diabetes insipidus and recommended that administration of pitressin be continued although he noted that it was not altogether successful in relieving the boy's symptoms.

The patient returned 2 months later complaining of continued pain over the right eye and of failing vision The ocular fundi appeared normal At perimetry a central scotoma was demonstrated in the field of each eye (Fig. III–7) indicating involvement of both optic nerves Roentgenographic examination of the head was repeated and was interpreted by the roentgenologist on that occasion as showing an erosion of the floor of the

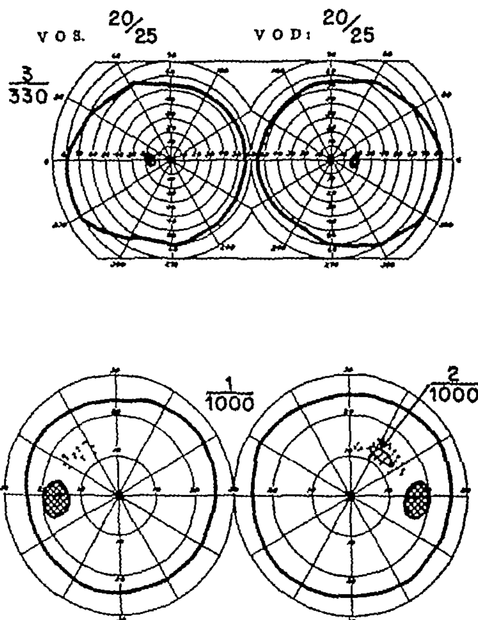


FIG. III-6. (case 4) Relative scotomas in the fields of both eyes

sella turcica by a primary intrasellar tumor The neurosurgeon who was called in consultation made a tentative diagnosis of Rathke-pouch tumor, probably on the basis of the patient's age, and advised left transfrontal craniotomy He carried out this operation a few days later and exposed a large purplish cellular tumor, which completely encircled the left optic nerve spread out into the left middle fossa, filled the sella turcica and extended above the sella and underneath the right optic nerve He was able to remove most of the tumor tissue The pathologist's diagnosis was cellular active chromophobe adenoma Because of the nature of the tumor, a course of deep roentgen therapy was administered. Perimetric fields were charted 1 week after operation and were found to have returned to normal.

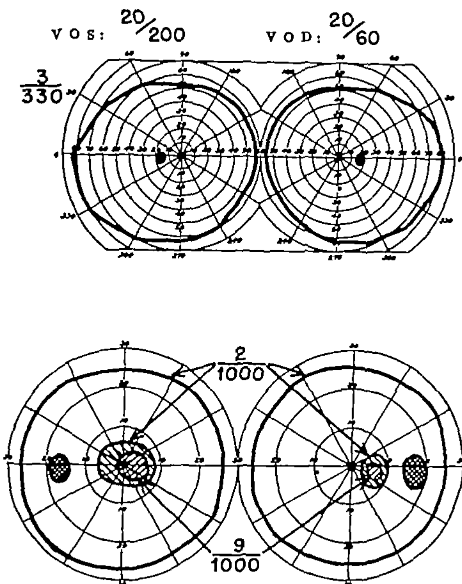


FIG. III-7 (case 5) Bilateral central scotomas

The patient has returned at yearly intervals for the past 9 years and to date the visual acuity and the visual fields have remained normal. He is now 20 years old and feels well although he has not developed a beard or axillary hair He is taking cortisone desiccated thyroid pitressin powder and testosterone

Pressure on an optic tract produces incongruous homonymous hemianopsia that is defects in corresponding half fields that are dissimilar The charts of such fields are not superimposable

Case 6— A 44-year-old man complained of headache He said that 8 years previously he had noticed a gradual enlargement of his hands feet and mandible and recalled periods of drinking excessive amounts of water

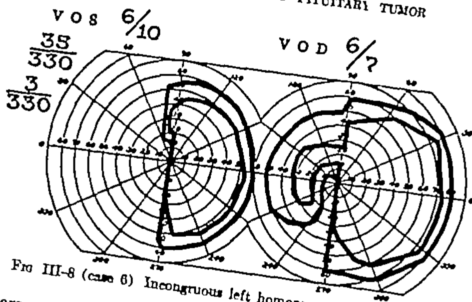


Fig III-8 (case 6) Incongruous left homonymous hemianopsia

Four years previously a physician had told him he had trouble with his pituitary gland, and 6 months previously he had had roentgen treatment directed to it Recently there had been headaches and nausea

Visual fields (Fig III-8) showed incongruous left homonymous hemianopsia indicative of involvement of the right optic tract Roentgenographic examination of the head showed considerable enlargement of the sella turcica especially on the right side, and evidence of associated acromegaly Since operation was not performed, this is not a proved case, yet there can be little question that this is an excellent example of incomplete interruption of the right optic tract

The dissimilarity in the homonymous defects need not be as extreme as these In the following case there was less incongruity

Case 7— A 50-year-old woman complained of a vague disturbance of vision which she had noticed for 1 year and a definite clouding of vision for 2 weeks Ophthalmoscopic examination showed a mild pallor of both optic disks Visual fields (Fig III-9) showed an incongruous left homonymous hemianopsia which the perimetrist interpreted as indicative of involvement of the right optic tract Roentgenographic examination of the head showed decalcification and erosion of the anterior floor of the sella turcica and of the anterior clinoids, due to intrasellar tumor with suprasellar extension General and neurologic examinations did not reveal abnormalities Preliminary right carotid arteriography disclosed a slight elevation of the right anterior cerebral artery The neurosurgeon, by way of a right transfrontal craniotomy exposed the optic chiasm and found underneath it a large tumor which had extended backward and displaced the right optic tract upward The tumor a chromophobe adenoma, was thoroughly removed.

Nine days later visual fields were charted again and found to be greatly

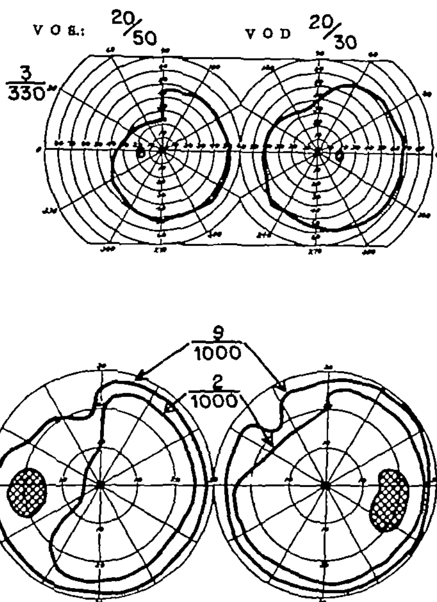


FIG. III–9 (case 7) Incongruous left homonymous hemianopsia

improved (Fig. III–10) Three months later when the patient returned for observation the fields were almost normal and the patient said she felt well There has been no subsequent follow up

Another example of involvement of an optic tract is the following.

Case 8—A 54-year-old farmer 1 year before we saw him had been told that he had a pituitary tumor His visual fields were normal at that time On admission his complaint was loss of vision. His right optic nerve head was slightly pale and perimetric fields (Fig. III–11) showed a right lower quadrant homonymous hemianopsia so incongruous as to indicate involvement of an optic tract in this case the left Roentgenographic exam

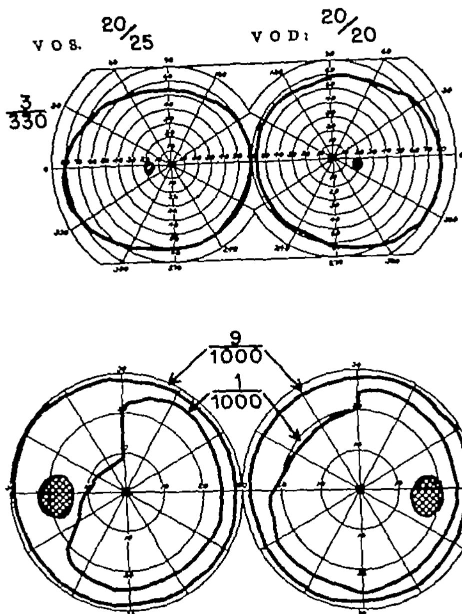


Fig III-10 (case 7) After operation

mination of the head showed erosion of the sella turcica and of the clinoids by and intrasellar tumor with suprasellar extension A partial paralysis of conjugate gaze to the right pointed to a disturbance in the pons, further evidence of extension backward of the tumor

The neurosurgeon found and removed a chromophobe adenoma which had grown backward under the chiasm and extended behind it. Postoperative check of the eyes showed greater defects than had been present previously (Fig. III-12) There was bitemporal hemianopsia plus a large loss centrally in the left eye Vision continued to deteriorate Four years after operation the left eye was blind

Late in the course of pituitary tumor the loss of vision is the result

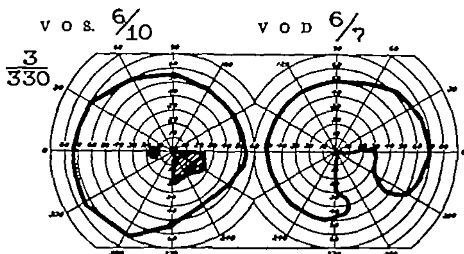


FIG. III-11 (case 8) Incongruous right lower quadrant homonymous hemianopsia

not only of pressure on the part of the tumor itself but of displacement of the chiasm upward against the arterial arch of the anterior portion of the circle of Willis. The constant hammering of the arteries may cut deep grooves in the chiasm and destroy nerve fibers previously spared by the lesser pressure of the tumor earlier in its course.

During recent years the skill of the neurosurgeons has so improved that no specimen of this has come to my attention for some time For an example I have had to resort to a case previously reported (6)

Case 9—The patient was a 56-year old man who complained of blindness of his left eye He stated that vision of the left eye had become blurred 1 year previously about a month later the eye suddenly became blind. At the same time he had noted an intense headache which had lasted several

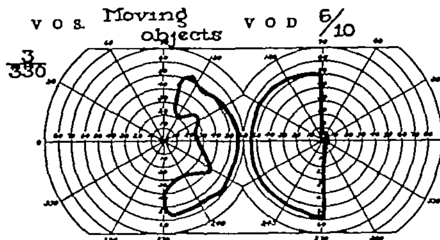


FIG III-12 (case 8) Bitemporal hemianopsia after operation

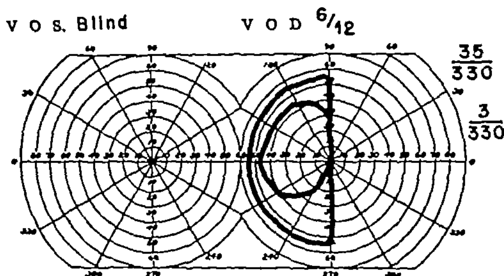


Fig III-13 (case 9) Blindness of left eye loss of temporal half of field of right eye (6) (From Rucker and Kernohan by permission of the A.M.A Archives of Ophthalmology)

days. On being questioned, he admitted intolerance to cold for 2 years and loss of strength and potency

On examination, the acuity of the right eye was 6/12 and its field (Fig III-13) was contracted temporally, the left eye was blind The optic disks were pale, and the left third cranial nerve was paralyzed Roentgenograms of the head disclosed great enlargement of the sella turcica by an intra sellar tumor, with suprasellar extension The clinical diagnosis was chromophobe adenoma of the hypophysis.

The neurosurgeon performed a transfrontal craniotomy and encountered a huge cystic mass containing blood, this mass was situated between the optic nerves. He was unable to determine whether it was an aneurysm or hemorrhage into a pituitary tumor, no attempt at removal was made. The patient died 2 days later

At necropsy, the tumor and overlying structures were removed The position of the anterior cerebral arteries and the grooves in the chiasm produced by them are shown in figures III-14 and III-15

APPEARANCE OF THE OPTIC NERVE HEADS

In the pituitary tumor the optic nerve heads retain a normal *pink color* until visual loss has been present for at least several months In some exceptional cases the nerve heads are pink even after a known visual loss of several years Pallor occurs much more quickly after trauma to the nerves, in a few reported instances as early as 3 weeks.

From a clinical viewpoint most patients with pituitary tumor exhibit



FIG. III-14 (case 9) Pituitary tumor underlying the optic nerves and chiasm and anterior cerebral arteries. Above is the tuberculum sellae turcicae (6) (From Rucker and Kernohan, by permission of the A.M.A. Archives of Ophthalmology.)



FIG. III-15 (case 9) Same specimen as in Figure 14 showing grooving produced by the overlying arteries (6) (From Rucker and Kernohan by permission of the A.M.A. Archives of Ophthalmology.)

some pallor of their optic disks its intensity being governed by the amount and the duration of the visual loss There is much individual variation

Pallor has definite value in prognosis nevertheless When the nerve heads are pink even if visual loss has existed for many months there is a good chance for improvement in visual fields and even a return to normal following eradication of the tumor When the nerve heads are slightly pale

and the visual loss is relatively great, improvement may be expected and perhaps even a slight lessening of the pallor When the nerve heads are distinctly pale, improvement in vision is not to be expected, although partial return is noted occasionally

When the disks are pale and, in addition, there is visible loss of nerve substance, then true optic atrophy exists and there is little possibility of recovery of any vision or of diminution of the pallor of the disks

The pallor of the nerve heads may be explained by a constriction of their capillary network. In any nervous tissue the volume of the blood supply is determined by functional activity When function ceases, as in interruption of the optic nerves, a lessened amount of blood is required and a physiologic constriction of their capillaries ensues This is evident on ophthalmoscopic examination by the fading away of the capillary network on the disk Another factor, probably of less importance, is the proliferation of glial tissue that follows the death and degeneration of nerve tissue

Papilledema very seldom occurs in cases of pituitary tumor When it does, it is a late finding and indicates invasion of the third ventricle.

PARALYSIS OF OCULAR MUSCLES

Paralysis of the extra ocular muscles is infrequent in adenoma of the pituitary, Bardram (1), for example, found 8 instances in 90 verified adenomas, Chamlin, Davidoff and Feiring (3) found 8 in 109, Barrett (2) noted 9 in 308 A rough estimate of the incidence may be 5 to 10 per cent, although my personal observations would lead me to a number some what less than 5 per cent.

In a group of 15 cases that have come to my attention during the past 10 years, the third nerve was involved in every instance, in 9 it was the only motor nerve to the eye to be affected, in 3 instances the third and the fourth nerves were affected, and in 3 others the third, fourth and sixth nerves. In this group of cases there was not a single example of paralysis of the fourth or sixth nerve without the third nerve also being paralyzed

The oculomotor nerves are protected from lateral pressure of the expanding tumor by the carotid artery Paralysis of the extra-ocular muscles indicates intracranial extension of the tumor and nearly always a relatively malignant growth and an unfavorable prognosis.

An example of implication of the third nerve follows

Case 10—A 58-year-old man complained that for 6 years he had been tired all the time Weakness in his legs had given difficulty in going up stairs He had no headaches The consultant in metabolic diseases noting his pasty color smooth dry skin and sparse axillary hair, made a diagnosis of mild pituitary insufficiency Visual acuity and visual fields were normal.

When the patient returned 7 months later he complained that for 2

months he had suffered from repeated cramps in his legs and four or five episodes of blurred vision of about 1 hour each. Roentgenographic examination of the head showed enlargement of the sella turcica with elevation of the right posterior clinoid by intrasellar tumor with extension to the right side. Charting visual fields demonstrated a bitemporal hemianopsia (Fig. III-16) Treatment consisted of irradiation of the region of the pituitary with the cobalt 60 teletherapy unit.

A month later the patient began seeing double as a result of partial paralysis of the right third nerve The defects in the visual fields were unchanged The neurosurgeon, through a right transfrontal craniotomy, found a laminated pituitary adenoma of moderate size, which he was able to remove. He was not able to explain the paralysis of the third nerve by the location of the tumor, and tentatively assumed that there had been an

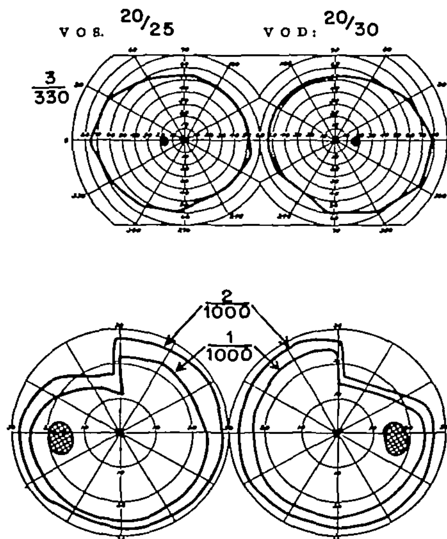


FIG. III-16 (case 10) Bitemporal depression

extension of the tumor which he could not see A week later the defects in the fields and the third nerve paralysis had lessened

Nine months later, on the occasion of the patient's most recent visit, visual fields were normal and the weakness of muscles supplied by the third nerve was minimal There was no diplopia The patient still tired readily, and was receiving cortisone, thyroid and testosterone.

When the nerves to the muscles of the eyes are involved by pituitary tumor, the tumor is usually large and rapidly growing.

Case 11—A 47-year-old man was first seen in August, 1950, when he complained of intense intermittent pain at the apex of the right orbit which had been present for 1 month He stated that he saw double from time to time, but we were not able to demonstrate any weakness of the eye muscles The ocular fundi appeared normal and the visual fields were full Roentgenographic examination of the head showed extensive destruction of the sella turcica, especially on the right side. An arteriogram was negative The neurosurgeon then explored the region of the chiasm and demonstrated a mass between the right optic nerve and the central carotid artery, tissue from it was recorded by the pathologist as "inflammatory "

During the following 2 years the patient suffered from headaches of moderate intensity and generalized weakness.

He returned in October, 1952, complaining of double vision, which was found to be due to a partial paralysis of the right third nerve On November 3, 1952, a defect in the visual field was demonstrated for the first time, a bitemporal depression (Fig. III–17), indicating an involvement of the optic chiasm. On November 6, a second transfrontal craniotomy was performed and an extensive tumor mass was encountered, a specimen of it

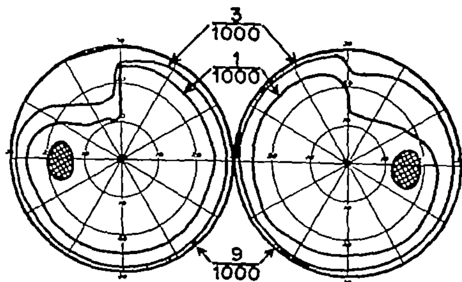


FIG. III-17 (case 11) Bitemporal depression

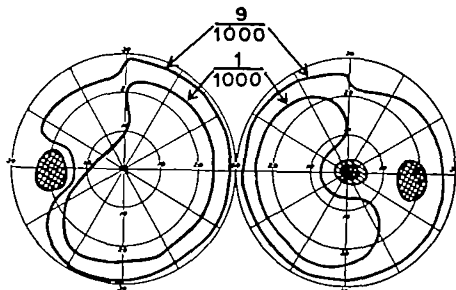


FIG III-18 (case 11) Bitemporal depression and central scotoma

was reported by the pathologist to be chromophobe adenoma of the pitui tary Postoperatively there was complete paralysis of the right third nerve

The following year, in August 1953, when the patient returned for ob servation, the defect in the visual field was unchanged, but there was a complete paralysis of the right third and sixth nerves with sparing of the fourth nerve and also a paralysis of the right side of the face By November of that year, the condition had become worse and the defect in the field was more extensive than it had been previously (Fig III-18) At that time there was a complete paralysis of the third fourth sixth and seventh nerves The patient received roentgen treatment but responded poorly and died in 1955

In this case the early involvement of the third nerve warned that the growth had already extended out of the sella turcica that it was more malignant than most, and that the outlook was discouraging.

In several cases paralysis of the third nerve has appeared after the intra cranial operation. An example follows

Case 12—A 41 year old man complained that his vision had been failing for 6 months. Ophthalmoscopic examination disclosed a mild pallor of both optic disks On charting perimetric fields (Fig. III-19) there was demon strated a bitemporal hemianopsia Roentgenographic examination of the head showed the sella to be enlarged by an intrasellar tumor Operation was advised and carried out and the neurosurgeon removed a chromophobe adenoma Six days later the patient complained of seeing double and there was found to be a complete paralysis of the right third nerve It was as sumed that the paralysis was probably due to edema of the brain and

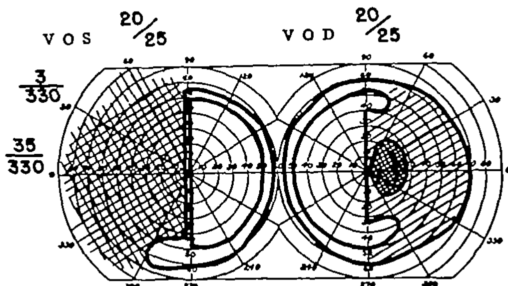


Fig III-19 (case 12) Bitemporal hemianopsia

herniation of the hippocampus with pressure of the third nerve against the edge of the tentorium

When the patient returned 3 months later, the visual fields were greatly improved (Fig III-20) and the paralysis of the third nerve had lessened, there being at that time only a wide pupil and slight weakness of the superior rectus and the inferior oblique muscles.

After another 6 months the patient returned for observation once again Visual fields were unchanged, but the paralysis of the third nerve had completely disappeared.

Oculomotor paralysis as a postoperative complication does not carry the ominous implication of such a paralysis seen preoperatively

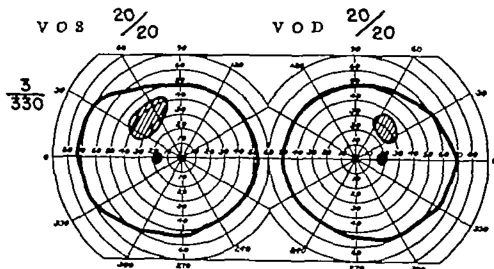


Fig. III-20 (case 12) Bitemporal scotomas

DIFFERENTIAL DIAGNOSIS OF CHIASMAL LESIONS

Adenoma of the pituitary is by far the most frequent tumor in the region of the optic chiasm. Other types of lesions to be differentiated are numerous, yet each individually is uncommon.

Adamantinoma belongs near the top of the list. Visual loss occurs early and is the presenting symptom in half the cases. The defects in the fields tend to be irregular and asymmetrical, and may be bitemporal or homonymous. The roentgenologist is often able to make the diagnosis on the basis of suprasellar calcification.

A meningioma arising at the tuberculum sellae may produce bitemporal hemianopsia, one arising at the medial portion of the sphenoidal ridge may produce loss of vision in only one eye. Symptoms are restricted to loss of vision until late. Too often, roentgenograms fail to show evidence of the growth, and neurologic examination fails to show any other abnormalities. Then the neurosurgeon may be forced to rely solely on the findings of the ophthalmologist.

Astrocytoma of the chiasm occurs usually in childhood and is sometimes associated with café au lait spots and neurofibromatosis. Visual loss is early and may be rapid, the defects in the fields are often bizarre. There are no symptoms except loss of vision until late, when the growth extends into the third ventricle and the hypothalamus.

Still more rarely the malignant lesion may be a chordoma, a pinealoma or a carcinoma of the sphenoid or may even be metastatic as from a breast or a lung. It is because of this wide range of possibilities that a comprehensive examination is advisable in every case of involvement of the chiasm.

An aneurysm of the circle of Willis may press against the optic chiasm, producing a visual loss that is characteristically abrupt in onset, irregularly progressive and fluctuating in its course with intervals of partial recovery. The field defects are asymmetrical, since the aneurysm is seldom at the midline. There is likely to be pain localized behind the eye.

A blow on the head may cause bitemporal hemianopsia; the history of injury is so obvious that there should be no difficulty in its differentiation from pituitary adenoma.

Chiasmal arachnoiditis is a real enough entity, but in my experience a rare one. I have encountered a few surgically proved cases due to syphilis, a few presumably due to tuberculosis and a few of nonspecific etiology. Each presented chiasmal field defects and was explored in order to investigate the possibility of a new growth. In most instances the diagnosis had been suspected prior to operation. There is nothing of specific diagnostic value in the visual fields.

Dilatation of the third ventricle through increased intracranial pressure may result in chiasmal or prechiasmal field defects by stretching or dis

placing the chiasm or by interfering with its blood supply In this condition the optic disks are always choked This one finding is sufficient for differentiating dilatation of the third ventricle from a pituitary tumor, since the optic disks are normal or atrophic in pituitary tumor

CONCLUSIONS

The diagnosis of pituitary tumor cannot be made by the ophthalmologist alone He can report involvement of the optic chiasm, and can name with considerable accuracy the portion of the chiasm affected, whether it be to one side or the other or anterior or posterior, but usually he must leave to others the determination of the nature of the lesion and the extent to which other structures may be implicated His finding of an occasional case of paralysis of one of the motor nerves to the eyes gives helpful information regarding extension of the tumor

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Questions and Answers

Question What is your opinion regarding further loss of vision from a surgical procedure or from roentgen therapy, and what is meant by sufficient visual improvement and sufficient visual loss?

Dr. Rucker Speaking as an ophthalmologist, I would say that any degree of visual loss is serious We regard it as very serious, even if there is only a minute defect in the upper temporal portion of the field. I have been an interested bystander in this for a long time. At times I have wondered what would be the best way to handle pituitary tumors, but that was never my direct responsibility I happen to work in a clinic in which, in the early days, at least, the emphasis was largely surgical. I am

sure that our attitude there is influenced somewhat by this emphasis on surgery. Consequently, most of our patients are treated surgically. For a year or so, I have been reading various papers on this subject by neurosurgeons. It seems to me that in this problem one series of patients cannot be compared with another series. For instance, in one institution surgical treatment is preferred, whereas in another institution roentgen ray therapy is used. It is not possible, so far as I can see, to compare successfully the results of one institution with the results of another institution. Neither can we compare—for the purposes of our work—patients who have been operated upon with those who have not been operated upon. In former years, at least, patients who were not operated upon did not come to operation for rather definite reasons—either the surgeons felt the patients were too ill to withstand the stress of surgery or there was no very definite visual loss or some special consideration supervened. Hence we actually have no series which we can compare, one with the other, as "surgical" and "nonsurgical." I find that our surgeons of considerable experience, such as Dr. Love, are more inclined toward operation, while I notice that some of the younger ones prefer roentgen ray therapy. I am going to be very much interested, in the years ahead, to see what the results of the two attitudes will be.

Regarding the other part of the question, it is true that some patients exhibit larger defects in the visual fields after operation. Still I would say that most of them show improvement after operation. Some patients, who appear to be a little worse after operation, experience their improvement during the succeeding months. Once in a while, surely, we do see some defects that are rather large after operation. I demonstrated one or two of them to you a couple of days ago in my talk on hypophysectomy in the absence of tumor. It is true that we see defects in the visual field after that type of operation also. In most cases we are careful to chart the visual fields prior to operation so that postoperatively we shall have data for comparison.

QUESTION: *Is there some way to interest ophthalmologists in neuro-ophthalmology in order to obtain competent field studies?*

DR. RUCKER: Those ophthalmologists who were so unfortunate as to have taken their training in institutions in which they saw largely ophthalmic surgery and diseases of the eyes naturally became more interested in refractions and removal of cataracts and treating glaucoma and such diseases. That is not quite as true, [illegible] w as it was years [illegible] w the ophthalmic board requires ophthal[illegible] to undergo ex[illegible] s in neuro-ophthalmology and a special [illegible] on in peri[illegible] hat most younger ophthalmologists prob[illegible] ad adequat[illegible] n perimetry. So far as I know, most of t[illegible] s *from* w[illegible] me teach

a fair amount of perimetry and neuro-ophthalmology As I have visited various parts of the country I have found that residents in neurosurgery in many cases were examining visual fields themselves. The neurosurgeon in charge of the service did not call on the ophthalmologist Possibly this was because he had not been able to obtain the kind of help he wanted on previous occasions, but as he was not in the habit of calling ophthalmologists for the work, the residents in ophthalmology did not have access to neurosurgical patients to carry out the examinations in question Perhaps neurosurgeons could improve the situation by calling for an ophthalmologist once in a while to examine some neurological patients In this way resident ophthalmologists might become interested in the perimetry I think the eventual development of such rapprochement would work an advantage to both fields. Meanwhile, I am sure the younger ophthalmologists are more competent in this regard than ophthalmologists were in previous years, and they can do perimetry for you, so that you need not resort to doing this type of examination yourself

DR. RAY Too often in my vicinity, when we get visual fields from an ophthalmologist—even in the University Ophthalmological Department—the best has been done by technicians. Visual fields take time, and it is hard to induce an ophthalmologist, in his busy day, to do the kind of fields that a neurosurgical resident will do

DR HORRAX That is exactly my experience, we haven't an ophthalmologist at the Lahey Clinic We send patients whom we feel need special types of field studies or any other types of visual diagnosis to some of the neighboring ophthalmologists. However, our fellows do the ordinary visual fields or we do them ourselves. I would agree with Dr Ray, that often ophthalmologists do not obtain as satisfactory fields as you would from some of the residents.

DR. RUCKER We are very well aware of this problem It is one aspect of ophthalmologic practice that must be improved, but I am confident it will be

QUESTION TO DR. PENFIELD Could you comment on the problem of x-ray therapy and neuro-ophthalmology in the treatment of pituitary tumors?

DR. PENFIELD In regard to the problem of roentgen therapy, I haven't anything to add However my experience with ophthalmologists has been quite different When a patient returns to his home which is a long distance away we ask some ophthalmologist in his home town to give us regular reports of visual fields. In my opinion our experience is a very happy one and the ophthalmologist's willingness to cooperate with us is a bit higher than has been expressed. As far as loss of vision is concerned, I would just add that it is not a question of the level of visual acuity, but rather a question of the rate of the loss of vision that should cause the neurosurgeon

to become alarmed. Above all, we must keep the conception that pituitary tumors are neurosurgical problems and must be handled and followed by neurosurgeons, whatever the method of treatment may be This series that Dr Horrax has studied and reported to us is, in my opinion, the best studied series in existence, and I think that each of us in handling these cases should try to follow his outline as carefully as we can.

QUESTION TO DR. HORRAX How often do you see a pituitary tumor extend beyond the sella without visual changes or extraocular disturbance?

DR HORRAX I think that is rare Off hand I don t recall any case of a pituitary adenoma coming into that category On the other hand, we see many people with certain endocrinological stigmata and an enlarged sella turcica who do not have any visual changes whatever, but I don't know of any that have extended beyond the sella without causing visual changes.

DR. RUCKER I have no way of arriving at an opinion on that point, but so far as I know our surgeons do not operate on patients for lesions around the optic chiasms unless there is a defect in the visual fields

QUESTION In traumatic amblyopia associated with basofrontal fracture, where the fracture goes through the optic foramen, what is the prognosis for the return of vision?

DR. RUCKER I practice out on the prairies of Minnesota where, as a rule, we do not see many traumatic injuries of that nature. In respect to the ones I have seen, I would say that the progonsis is poor

QUESTION TO DR. LOVE Do you ever think it necessary to decompress an optic nerve?

DR. LOVE I would say that if there has been complete blindness, the prospects of restoration of vision by carrying out a transfrontal procedure and then elevating the fracture at the optic canal would be very slight. I think there would be no chance of restoring vision which was suddenly and completely lost. I have in mind however a very important case which I think was reported many years ago by Adson and Lillie I had the opportunity of examining the visual fields of this particular patient on many different occasions. She had sustained a fracture through the optic canal and progressive impairment of vision in that eye developed as the result of formation of callus. Dr Adson decompressed the optic nerve and the result was improvement in her vision. I think, however that sudden and complete blindness under the circumstances mentioned is comparable to the immediate traumatic paraplegia or quadriplegia caused by severe damage to the spinal cord. Restoration of vision is not likely, any more than return of nerve function is likely after damage to the cord.

CHAPTER IV

The Roentgenologic Aspect of Lesions About the Sella Turcica

JOHN D CAMP, M.D

DIFFICULTIES OF RECOGNIZING CHANGES IN THE SELLA

There are many lesions which influence the sella turcica and the optic chiasm. These differ greatly in their site of origin, history, symptoms, progress, and last but not least, their surgical operability In my opinion they also produce various changes in the roentgenogram which serve to identify at least some of them from each other

The normal sella turcica varies widely in size and shape So great is this variation that recognition of disease based on alterations of size alone is frequently difficult and even misleading. Rasmussen (1) has shown, also, that there is no constant relation between the size of the sella and the size of the pituitary gland This further decreases the value of measurements of the sella alone as an index of pituitary disease. My own experience indicates that in the past the average radiologist has paid too much attention to variations in the dimensions of the sella turcica and has underestimated the significance of certain basic changes in structure which will indicate the presence of disease long before measurements alone have any value These basic changes, erosion, decalcification and destruction of bone are intimately related to one another They may express themselves in focal or generalized changes in contour of the sella or its related processes depending on the type and location of the lesion. Erosion of the sella, or any of its related processes, is due to pressure from a contiguous mass abnormal pulsation or generalized pressure reflected from a more remote lesion. This focal or generalized pressure produces a loss of substance of the cortex of the exposed surface of the sella or contiguous processes. A certain amount of localized decalcification accompanies the pressure erosion, the degree being directly related to the site and severity of the associated pressure If the pressure is of a low degree and persistent, it may be reflected only in a change in contour of a single process or of the entire sella with little evidence of decalcification since in such cases there is a natural reparative recalcification at the site of erosion. On the other hand, if the pressure is acute severe, and progressive, erosion occurs rapidly without opportunity for repair by recalcification and the picture is soon one of complete loss of bone substance, either focal or generalized.

Classical examples of true decalcification of bone are seen in severe infections of the sphenoid sinus and in varying degrees in the presence of contiguous meningiomas In the former, the decalcification results from hyperemia of the walls of the sphenoid sinus which accompanies the infection, in the latter it results both from hyperemia due to increased vascularity at the site of a tumor and from actual pressure by tumor cells which grow into the haversian canals of the adjacent bone.

Actual invasive destruction of the sella or its related processes occurs with malignant tumors which may originate in the bony structures or involve them secondarily by extension from a contiguous soft tissue mass Such changes because of their location and extent are usually not difficult to distinguish from erosion incident to benign lesions. Extensive pressure erosion of the sella resulting from large pituitary tumors or generalized increased intracranial pressure may be imitated by a malignant lesion of the sphenoid bone such as chordoma, myeloma or carcinoma.

In any discussion relating to erosion, decalcification or destruction of the sella, definite evidence indicating the relation of such changes to the duration of the primary disease is of great value On the basis of my own experience I believe that one can conservatively say that in the presence of increased intracranial pressure erosion or decalcification of the sella may occur within one month after the inception of abnormal pressure The ability of the roentgenogram to reveal this change is dependent on the type of sella and whether or not it is undermined by a well pneumatized sphenoid sinus If the sphenoid below the floor of the sella is not pneumatized (and it frequently is not in children before the age of twelve years), erosion of the floor may not be recognized until more extensive changes have occurred

ROENTGENOGRAPHIC RECOGNITION OF SELLAR CHANGES

Roentgenographic technique plays an important part in contributing to the early recognition of changes in the sella and its related processes. Stereoscopic roentgenograms are necessary but in order to be of the greatest value in this area, these should be made with the tube shifted along the coronal plane The shift of the tube will separate the images of the clinoid processes and the edges of the sella, a very important maneuver since it facilitates the recognition of focal changes which may involve only one process or side of the sella. This is clearly shown in Figure IV-1, in which the focal erosion and foreshortening of the right anterior clinoid process was due to an aneurysm of the internal carotid artery When such changes are observed the roentgenologist can be very precise and exact in the location of a lesion. The mechanics of this erosion are shown in Figure IV-2 a case in which the walls of an aneurysm of the internal carotid

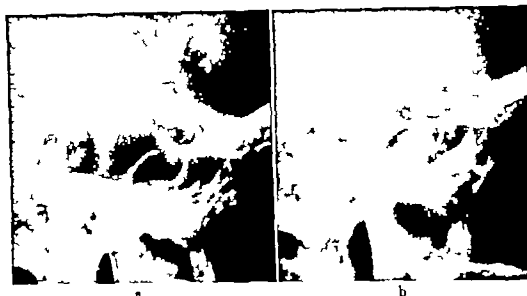


FIG. IV-1 Stereoscopic lateral views of the sella, indicating the value of shifting the x-ray tube along the coronal plane a (left) The images of the anterior clinoid processes which are superimposed, appear normal. b (right) After shifting tube, images of anterior clinoid processes are separated focal erosion and foreshortening of right anterior clinoid due to pressure from a contiguous aneurysm of the right internal carotid artery are evident.



FIG IV-2 Lateral view of sella revealing focal erosion and foreshortening of the right anterior clinoid process due to pressure from a contiguous calcified aneurysm of the right internal carotid artery



FIG. IV-3 Stereoscopic lateral roentgenograms of the skull. a (left) Images of the anterior clinoid processes are superimposed and therefore appear normal. b (center) Images of anterior clinoid processes have been separated by shift of tube along coronal plane c (right) Postero-anterior view revealing decalcification of right anterior clinoid process due to meningioma of the right sphenoidal ridge

artery are partially calcified. Foreshortening of the contiguous anterior clinoid process due to pressure erosion may be seen At the point of contact with the wall of the aneurysm the cortex of the anterior clinoid process has disappeared as a result of pressure and decalcification. Normally the clinoid processes are outlined by a shadow of thin cortical bone. Dehiscence in this shadow is the first indication of contiguous pressure

The images of the anterior clinoid processes are superimposed in Figure IV-3a and no abnormality is evident. However, in Figure IV-3b which is the matching stereoscopic film the images of the anterior clinoid processes are separated and it is obvious that there is a great difference in density between them. The same difference is also apparent in Figure IV-3c, which is a postero-anterior view In this case the tumor cells from an adjacent meningioma invaded the bone and with the associated increased vascularity, have produced diffuse decalcification which results in a diffuse hazy image in contrast with the focal type of pressure erosion shown in Figs IV-1 and 2 Therefore the roentgenologist, if he has good roentgenograms and has had reasonable experience may be able to predict the type of contiguous lesion from the observation of such changes The postero-anterior 107 degree angle view originated by Granger (2) for depicting disease of the sphenoid sinus is valuable also for revealing and lateralizing focal changes resulting from lesions about the sella tuberculum or optic nerves. Local changes in bone which consist of defects in continuity (Fig.

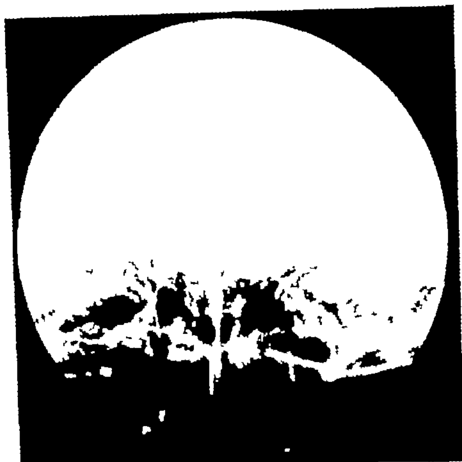


FIG. IV–4. The postero-anterior 107-degree projection of skull (Granger position) revealing focal erosion and defect in continuity of the so-called g line as the result of a contiguous meningioma of the left optic nerve sheath

IV–4) or abnormal thickening (Fig. IV–5) of the so called g-line may be more clearly defined in roentgenograms obtained in this position than in conventional lateral or postero-anterior views. The osteomatous changes resulting from meningiomas arising about the tuberculum sellae and posterior portion of the olfactory groove may be seen very clearly in the views taken in the Granger position. Such tumors as they enlarge frequently produce erosive changes in the floor of the sella and posterior clinoid processes

Erosion of the posterior clinoid processes may be the result of 1) direct pressure from a contiguous tumor most commonly a partially calcified craniopharyngioma (Fig. IV–6), 2) pressure from a dilated third ventricle (Fig. IV–7), and 3) mass lesions of the brain (without hydrocephalus) which produce indirect pressure on the clinoid processes and sella.

In the past it was not uncommon for roentgenologists to accept the presence of decalcification and circular expansion of the sella as evidence of a primary intrasellar tumor, (Fig. IV–8) Experience has shown, however that these changes may be produced also by tumors located else-

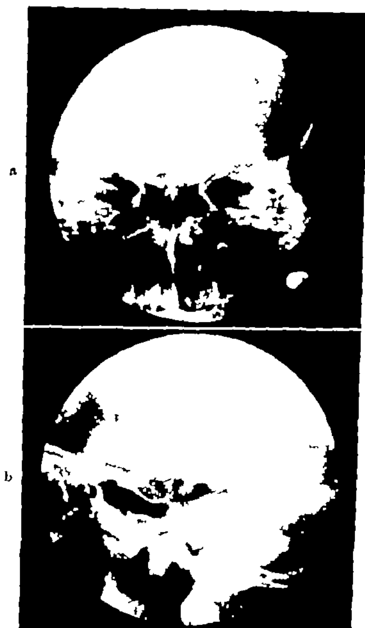


FIG. IV-5 Meningioma arising from tuberculum sellae. a. (top) Postero-anterior *view of skull revealing osteomatous thickening of so-called g-line at site of tumor* b (bottom) Lateral view of sella, revealing osteoma at site of origin of tumor and early pressure erosion of floor of sella

where in the cranial cavity (Fig. IV-9) In such cases a displacement of the shadow of the calcified pineal gland or evidence of generalized increased intracranial pressure will provide a clue to the extrasellar location of the lesion. Such evidence may of course, be lacking and therefore it is important to remember that whenever the roentgenogram suggests an intrasellar tumor and the clinical evidence does not agree, additional

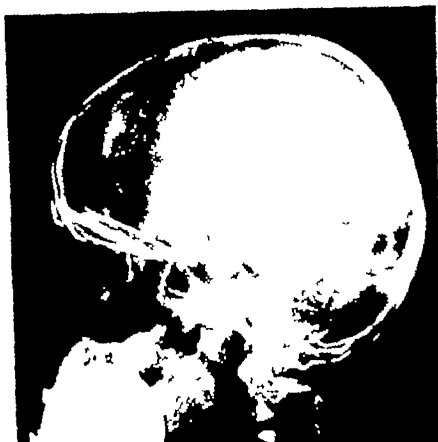


FIG. IV-6 Calcified craniopharyngioma producing focal erosion of the posterior clinoid processes and dorsum sellae



FIG. IV-7 Ventriculogram revealing dilated third ventricle with erosion of posterior clinoid processes and sella as a result of hydrocephalus due to a cerbellar tumor

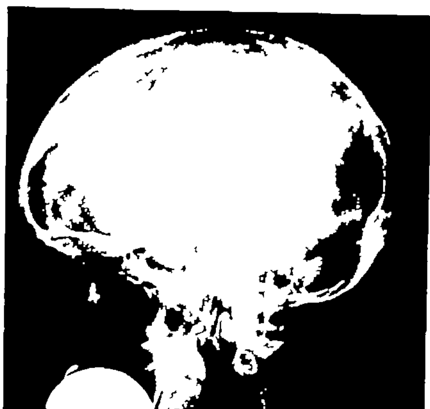


Fig IV–8 Circular expansion and decalcification of the sella produced by primary intrasellar pituitary tumor

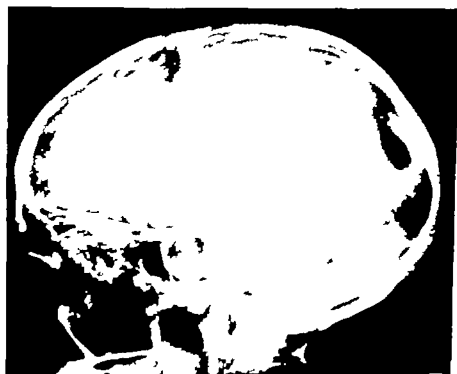


Fig IV–9 Circular expansion and decalcification of the sella produced by right temporal lobe tumor The changes simulate those of intrasellar tumor



FIG IV-10 a (top) Invasion of sphenoid bone and destruction of posterior portion of sella caused by lymphoepithelioma of sphenoid sinuses. b (bottom) Appearance of sella 5 months after radium treatment. Note recalcification and restoration of contour of sella.

methods of localization such as encephalography, ventriculography or arteriography must be considered.

The capacity of bone to recalcify after pressure on it has been relieved, or an invading tumor has been destroyed by radiation is well illustrated by the sella turcica and its related bony processes. Roentgenologic evidence of such recalcification is important evidence of a favorable response



FIG IV-11 Chromophobe adenoma of pituitary a (left) Decalcification and enlargement of sella before surgical removal of tumor b (center) Recalcification of sella 6 years after operation and roentgen therapy There was no clinical evidence of activity of tumor c (right) Extensive decalcification and further enlargement of sella due to recurrence of tumor 11 years after original operation and roentgen therapy

to treatment. This phenomenon is particularly well illustrated in radiosensitive malignant tumors of the sphenoid which invade and destroy the sella without actual enlargement of the pituitary fossa (Fig. IV-10) Since the sella is not expanded measurements are of no diagnostic value and the significant roentgenologic signs are those of destruction and subsequent repair of bone.

When the sella has been decalcified and enlarged by pressure from an intrasellar (Fig. IV-11a) or extrasellar lesion and the pressure has been subsequently removed by one means or another, the margins of the sella will recalcify but the pituitary fossa will maintain its abnormal size and shape (Fig. IV-11b) A roentgenogram always will reveal this evidence of antecedent disease and it should not be interpreted as evidence of an active process. In this connection serial roentgenographic studies made before during and subsequent to treatment are most important in the evaluation of the prognosis.

When an intracranial tumor recurs and the pressure phenomena of the original disease are re-enacted the sella which had recalcified following treatment of the lesion will again undergo decalcification and this important evidence of recurrence will be readily apparent if previous roentgenograms are available for comparison (Fig. IV-11a 11b and 11c) Here again it is the character and density of the bony margins of the sella and not primarily any variation in size that indicate disease

SUMMARY

In conclusion, I would like to emphasize 1) the importance of focal changes in the bony contour of the sella turcica and its related processes as an index of disease before any significant change in size of the sella

occurs, 2) the value of decalcification and recalcification of the contour of the sella in following the course of intracranial disease, 3) the fact that a circular, uniformly enlarged sella, long recognized as characteristic of a pituitary tumor, may be produced by tumors situated elsewhere within the cranial cavity, and 4) the indication for supplementary methods of localization such as ventriculography, encephalography and arteriography when the clinical and roentgenologic findings do not agree.

I believe that the radiologist and clinician should be concerned first with conventional roentgenograms of the sella and chiasmal area. If they do not give evidence of a lesion then one must consider what other procedure to use. Certainly if you suspect a chiasmal lesion, arachnoiditis or pseudo-tumor syndrome then a pneumoencephalogram would be more fruitful. However, when you consider the type of tumor seen most frequently in the parasellar region, and there is nothing to sway you from the clinical findings, I think that angiography has a greater chance of being helpful than encephalography Frequently you will have to use both.

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Questions and Answers

Question Have you ever seen a loose, eroded fragment of bone above the sella which simulated calcification within a pituitary adenoma?

Dr. Camp Yes, I have seen that and it is very easy to confuse calcification of a carotid artery with calcification of a chromophobe tumor Calcification in the latter does not occur very often—only in about 4 per cent of such tumors—in my experience. Fragments of detached bone may fool you and I don't know of any definite way to distinguish them, except that they are usually not as sharply defined or as sharply curvilinear in character as vascular calcification or calcification in the capsule of a chromophobe tumor

Question Can intrasellar pressure be differentiated from intracranial pressure by x ray alone?

Dr. Camp Nothing is 100 per cent in this business but I do think that in most cases it is possible, with good x ray films, to come pretty close to telling whether the changes result from a lesion within the sella or contiguous to it, or whether they are the result of pressure reflected from a general increase of intracranial pressure. There are a number of things that will help In the young individual, before suture union occurs you have separation of suture lines and variations in contour of the suture

shadows. In an adult there is thinning of the bones of the skull and particularly in the postero-anterior view you may see a thinning on one side of the calvarium You may also get a shift in the shadow of the pineal gland. Certainly, if the pineal gland shadow is displaced 1 cm. to one side or the other and the sella has a round configuration simulating that of erosion from a pituitary tumor, you would not make a diagnosis of a pituitary tumor I think if we consider all of the changes which may be present, it should be possible in most cases to differentiate primary intra sellar pressure from generalized intracranial pressure

QUESTION Please repeat the significance of a double contour of the floor of the sella

DR. CAMP Briefly, the sella, in the presence of a pneumatized sphenoid sinus should give a sharply outlined contour if the patient is properly positioned. When there is increased pressure within the sella itself or within the calvarium, the pituitary gland is pushed downward and that pressure will first produce a decalcification of the floor of the sella so that instead of being sharp and clean-cut like the wall of a normal ethmoid cell, the outline of the sella becomes fuzzy and indistinct and that produces a so-called double coutour If the pressure is relieved or the tumor is removed, the sella will recalcify but it will have a double contour and double density because it never goes back to its original shape again Occasionally, the false appearance of a double contour may be produced by a partial rotation of the head of the patient, and occasionally by variations in the pneumatization of the sphenoid itself Usually you can recognize that, but if there is any doubt a planigram will frequently help

QUESTION Have you seen a rounded calcification in the cavernous sinus without accompanying bone changes and in the presence of a normal angiogram? If so what is it?

DR. CAMP I have never seen one

QUESTION Please repeat the significance of a double contour of the floor of the sella

DR. CAMP Briefly, the sella, in the presence of a pneumatized sphenoid distinguishing and evaluating lesions about the sella but unfortunately encephalography is a mechanical procedure and good filling with air is dependent upon an adequate drainage of the subarachnoid spaces Because inadequate drainage is so frequent I think it is hazardous to be too positive about the presence of small suprasellar lesions from changes in an encephalogram alone If you have a unilateral alteration of the rostral sulcus and you can be certain that it is persistent from a study of stereoscopic films or planigrams then I think it is of value. Sphenoidal ridge tumors and even meningiomas of the tuberculum sellae are difficult for me to recognize in an encephalogram and certainly in attempting a diagnosis

of chiasmal arachnoiditis you may run into a trap because of incomplete drainage of the basal cisternae. There are so many ifs about it, that unless the changes in an encephalogram are very obvious and definite, I think the chances of recognizing a small lesion are really better with an angiogram.

QUESTION What causes the erosion of the clinoids and dorsum with increased pressure?

DR. CAMP It is a mechanical phenomenon It does not make any difference whether the increase in pressure is due to an internal hydrocephalus or whether it is due to the mass effect of a big tumor which has increased the size of the brain. The sella happens to be in the central portion of the skull and is very vulnerable to pressure wherever it may originate. The pressure causes a demineralization. If steady pressure is exerted upon any bone of the body and held long enough, demineralization of that bone will occur at the site of pressure. This has been seen many times in experiments The skull is a closed box and pressure from a tumor on one side of the brain is distributed rather generally throughout when the mass is large enough, so that the change from a large right occipital tumor for instance is not going to be much different from that caused by a large left occipital or left frontal lobe tumor There may be certain minor distinctions but basically the changes are about the same. If you observe the sella at autopsy you will see how the pituitary is pushed right down into the pituitary fossa by increased intracranial pressure.

QUESTION Does the nature of erosion of the clinoid processes help greatly in localizing a parasellar lesion?

DR. CAMP Yes, I think it does because if the erosion is unilateral you can lateralize the tumor Also, if it is not only unilateral but has involved an anterior clinoid process or involves only the posterior clinoid and the dorsum you have been more precise in localizing it, not only *as to the side* but also as regards the area of the lesser wing or the dorsum of the sella itself Such changes also help in distinguishing an intrasellar tumor from the usual parasellar tumor

QUESTION What is the significance of a lateral pineal shift of 5–6 mm in the absence of clinical symptoms?

DR. CAMP We are getting a little away from the chiasm but in the absence of clinical findings of any sort and no other x-ray *change* I would be hesitant about putting too much value on a 5 mm *lateral pineal shift* I believe however that a lateral shift of the pineal is much *more significant* than a forward or backward shift. A lateral shift occurs more frequently with a *temporal lobe* tumor than with a tumor located elsewhere. If the patient has only a *lateral shift* and there is reason to suspect a tumor I would bet on its being in the temporal area However I think

you have to be a little bit practical about it all too The shape of the head has some influence on the position of the pineal gland. The scaphocephalic will nullify the normal measurements in a fore and aft pineal localization. Similarly, a turricephalic skull will throw off the vertical measurements. An asymmetrically developed skull is likewise an exception I have seen one patient who had a hemi hypertrophy of the body in which the hemi hypertrophy of the brain caused asymmetry of the skull. The pineal and falx as well were over from the midline but that condition is not common and the physical appearance of the patient would keep you from accepting the lateral pineal shift alone as evidence of a tumor

QUESTION What about the roentgen therapy of pituitary tumors?

DR. CAMP With the advent of super voltage x ray and radio-active cobalt therapy, the results from the radiation treatment of pituitary tumor have been improved I think it is largely a matter of efficiently getting adequate dosage into the tumor You have the ever present problem of preserving vision and whether you give x ray therapy or not the patient should be very carefully followed. If the vision is decreasing, the pressure had better be relieved one way or another Dr Horrax has discussed the question of x ray versus surgery in Chapter VI so I think we had better let that answer suffice for now

CHAPTER V

Operative Approach to the Pituitary Gland

J Grafton Love, M.D

What I shall say does not necessarily reflect the attitude of my associates in the Section of Neurologic Surgery of the Mayo Clinic With 8 neurosurgeons having their individual services, there are bound to be differences of opinion regarding surgical technique. What is stated here is not meant to be considered as the only right way to handle a patient with a pituitary tumor but rather as a way that has proved satisfactory in my hands

The late Dr Charles H Frazier (1), of Philadelphia, introduced in 1913 a technique of approach to the hypophysis through the anterior cranial fossa, a modification of which is in rather general use today At that time Dr Frazier said the hypophysis was the last of the cerebral structures to come within the scope of surgical therapy The hypophysis had been considered 'noli me tangere' by the surgeon because of its deep location and surrounding important structures—the cavernous sinuses, the optic nerves chiasm and tracts and the internal carotid arteries

Marie(2) in 1886 had pointed out the etiologic relationship of acromegaly and perverted function of the hypophysis He gave the incentive to therapy of the hypophysis

There are two principal modes of attack on the deeply situated structure One is the intracranial approach and the other the extracranial or transsphenoidal approach

Horsley (3), in 1906, removed a cyst of the pituitary through the midcranial fossa after elevating the temporosphenoidal lobe. This approach is not very direct and necessitates too much traction on and elevation of the sensitive temporal lobe

According to Frazier (1) Krause in 1905, was the first to suggest approaching the hypophysis through the anterior cranial fossa by resecting the frontal bone and proceeding extradurally until the lesser wing of the sphenoid is reached at which juncture the dura is incised and the hypophysis is easily exposed.

Surgery of the hypophysis is said according to Frazier (1), to have had its advent in 1907 when Schloffer performed his first successful operation by approaching the hypophysis by the extracranial and transsphenoidal route However Frazier considered Schloffer s operation rather

crude and disfiguring Hirsch (4) introduced the endonasal approach, which still seems to be the best extracranial procedure.

There are two main objections to the extracranial operation first, the risk of infection from the mucous membranes (with the introduction of antibiotics, this objection was largely overcome), and second, the small exposure that is possible by this route Suprasellar and parasellar extensions of the tumor cannot be removed by this approach

Frazier's original operative approach to the hypophysis through the anterior cranial fossa was needlessly complicated, laborious and very likely to be disfiguring He resected an osteoplastic flap from the right frontal region, removed en bloc the supraorbital ridge with a portion of the roof of the orbit, later replaced, and rongeured away the remains of the orbital roof to the optic foramen He then opened the dura to expose the tumor and visual apparatus It is of interest that he used intratracheal anesthesia in his first case

Later Cushing, Adson, Naffziger and others modified the frontal approach into the more or less standard transfrontal craniotomy which is employed today

INDICATIONS FOR OPERATION ON THE PITUITARY GLAND

Indications for operation on the pituitary gland are as follows (1) To preserve and restore vision, (2) to relieve increased intracranial pressure that is when the tumor is suprasellar and compresses the third ventricle and in the rare case of intraventricular tumor, (3) to preserve life when the tumor is so large that it compresses a temporal or frontal lobe of the brain or obstructs the third ventricle

Before undertaking surgical treatment for a suspected pituitary tumor, it is essential to evaluate the patient s general and metabolical status as well as his ophthalmological neurological and roentgenological status.

The chromophobe adenoma the most common tumor of the pituitary requiring surgical treatment is often associated with hypopituitarism, and the degree of lack of function of the gland should be determined so that the patient may be adequately prepared for surgical treatment and a base line established so that postoperative therapy may be more satisfactorily planned.

Eosinophilic adenomas of the pituitary which rarely receive surgical removal because they rarely impair vision are often associated with adenomatous goiters which may be very large and may impair the patient s airway owing to compression of the trachea Occasionally the goiter may be hyperfunctioning

Usually if there are (1) a bitemporal visual defect (2) an enlarged and eroded sella turcica and (3) evidence of disturbed pituitary function the

diagnosis of pituitary tumor is well founded. However, other types of tumor may compress the pituitary gland, interfere with vision and erode the sella turcica. Such tumors are adamantinomas (craniopharyngiomas), epidermoids, meningiomas and aneurysms.

If there is a history of unilateral retro-orbital pain, third nerve palsy or unequal or unilateral erosion of the sella turcica, carotid angiography should be performed to exclude an aneurysm.

Choking of the optic disks rarely occurs with pituitary adenomas, therefore, if there is edema of the disks in a patient suspected of having a pituitary tumor, it is wise to perform ventriculography (Fig. V–1) to localize the lesion more accurately It may be a suprasellar adenoma blocking the third ventricle or a foramen of Monro, or rarely the adenoma may be situated in the third ventricle Edema of the disks is more common with adamantinoma.

In some cases of homonymous visual defect, particularly if there is unilateral erosion of the sella, angiography, air studies or both are indicated to exclude aneurysm, astrocytoma of the chiasm, parasellar tumor and temporal lobe tumor

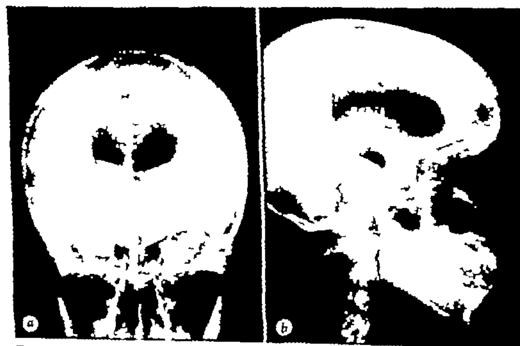


FIG V–1*a* The anteroposterior ventriculographic projection, showing *internal* hydrocephalus with tenting of the third ventricular shadow due to a large suprasellar adenoma of the pituitary The tumor caused marked distortion of the *third* ventricle with sufficient blockage of the ventricular system to produce obstructive hydrocephalus. Fig. V–1*b* Same case as V–1*a* showing lateral view of head *after* substitution of air for fluid in the ventricular system The enlarged eroded sella is visible The distortion of the third ventricle with enlargement of the lateral ventricles because of obstruction is obvious.

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FIG. V–1a. The anteroposterior ventriculographic projection, showing internal hydrocephalus with tenting of the third ventricular shadow due to a large suprasellar adenoma of the pituitary. The tumor caused marked distortion of the third ventricle with sufficient blockage of the ventricular system to produce obstructive hydrocephalus. Fig. V–1b. Same case as V–1a, showing lateral view of head after substitution of air for fluid in the ventricular system. The enlarged eroded sella is visible. The distortion of the third ventricle with enlargement of the lateral ventricles because of obstruction is obvious.

RESTORATION OF VISION

The best and quickest way to restore lost vision caused by pressure of a pituitary tumor on the visual apparatus is by surgical removal of the tumor For the surgeon who operates only occasionally on the pituitary, it may be best, if the visual loss is minimal, to try a course of roentgen therapy, then check the visual fields after 6 weeks, if the vision is not improved, he should consider surgical removal of the tumor While the therapy is being administered, if there is deterioration of vision, surgical intervention should not be delayed

In the presence of pallor of the optic disks and moderate-to-marked loss of vision, it is probably best to operate at once.

If there is sudden loss of vision, a bitemporal hemianopsia or complete loss of central vision in one or both eyes, emergency operation should be performed because of the possibility of hemorrhage into a pituitary tumor

When a decision has been made to operate for a pituitary tumor, the patient should be prepared with cortisone and suitable blood should be available for a transfusion It is the practice of my colleagues and myself to give 200 mg. of cortisone 2 days before operation 1 day before and the morning of operation This is administered intramuscularly Following operation, the patient receives cortisone in decreasing doses for a few days for example 100 mg the day after operation and 50 mg each day for 2 more days

EMERGENCY OPERATION FOR PITUITARY TUMOR

If it is necessary to operate on a patient for a pituitary tumor as an emergency procedure, then the intravenous preparation of cortisone may be administered during the operation.

The patient should be given a sedative the night before operation to insure a good night's rest I prefer pentobarbital sodium (nembutal) 1½ grains at bedtime for adults. All food and drink are withheld then until after operation. If the patient is to be operated on at 8 00 a m. he is given pentobarbital sodium 1½ grains and atropine sulfate 1/150 grain at 7 15 a m. and the head is completely shaved. For fussy patients a restricted shave may be used but it is necessarily messy and certainly increases the risk of infection

At 7 30 a m. the patient is taken on a cart to the operating room and anesthesia is induced I prefer to have the patient put to sleep with nitrous oxide and oxygen and then maintained during operation with open-drop ether over an intratracheal tube

Usually it is advisable in the absence of choked disks to use a malleable needle in the lumbar region for removal of cerebrospinal fluid to facilitate exposure of the tumor If a needle is to be used it is placed after the patient

is on the operating table After the needle has been placed and a clear flow of fluid has been assured, the needle is bent over against the back and connected by a long piece of rubber tubing to a 100-cc syringe so that at the proper time the anesthetist can remove fluid aseptically without moving the patient. The patient is then placed on his back with the head resting in a doughnut made of cotton wrapped with gauze The head is turned slightly to the side opposite the proposed flap The operating table is tilted slightly so that the head is higher than the buttocks. For a right handed surgeon the right transfrontal approach is best and it is safer for the right-handed patient, since the traction is on the nondominant hemisphere There are occasions, however, when it is necessary to operate through a left transfrontal flap For example, if the visual loss is principally in the left eye or there is a right homonymous hemianopsia, it may be impossible to reach the lesion from the right side

In marking the scalp for the flap the roentgenograms of the head should be on a viewing box in the operating room and they should be carefully studied The flap should extend down on the forehead as far as possible, but if at all possible one should avoid its entering the frontal sinus. If the sinus is unavoidably entered it should be closed immediately or if it is necessary in order to expose the tumor to open the sinus widely, it should be exenterated and obliterated by removal of the posterior wall If there is only a small perforation of the sinus, the hole should be plugged with bone wax and this should be covered with a piece of ivalon sponge or the dura should be pulled tightly against the opening by sewing the dura to the pericranium.

The flap (Fig V–2) used consists of a reflection of the skin and galea downward and forward through an incision starting in the midline of the forehead and proceeding backward to the hairline and then curving downward in front of the ear Adson skin clips are used on the edge of this flap to control bleeding, and small pointed forceps are used on the galea of the opposite skin edge The pericranium temporal fascia and temporal muscle are then incised around the edge of the flap and retracted for the making of five *perforator* openings For many years now I have used a perforator only rather than perforator and bur, in order to avoid unsightly depressions and the necessity of using anything to plug the bur openings The most important perforator opening is the one placed behind the zygomatic process of the frontal bone It should be placed as low as possible in order to facilitate exposure across the roof of the orbit At times it is advisable to nick the perforator opening with a DeVilbiss bone biter in order to hold the Gigli saw to the lowermost portion of the hole A corresponding nick in the anterior inferior (midforehead) perforator opening will at times enable the surgeon to avoid having to operate over a

is elevated and the dura is secured, a sizable extradural clot may develop As the fluid is removed from the lumbar area, the exposed dura and brain shrink (Usually 25 to 50 cc of cerebrospinal fluid is removed) It is preferable to expose the tumor by an extradural approach to the sphenoid ridge. If the dura has been extensively lacerated while the flap was being turned, it is just as well to proceed intradurally

By operating extradurally there is a flap of dura which protects the retracted frontal lobe, and there is less danger of a neurologic deficit, postoperative convulsions or both

The dura is dissected away from the roof of the orbit backward to the sphenoid ridge *It should not be opened until the ridge is reached.* An opening is made in the dura at the middle of the ridge with a right-angled knife cutting *toward* the *bone* Then the dura is opened to the midline and then upward parallel to the falx cerebri with dural scissors This incision is extended by making an opening in the dura over the tip of the temporal lobe with a *straight* knife and then cutting with scissors to the beginning at the middle of the sphenoid ridge The dural edges particularly those below, should be coagulated for they have a tendency to bleed

The frontal lobe, protected by the flap of dura, is then elevated with a ganglion light while the fluid beneath the brain is aspirated with the suction apparatus The first nerve to be seen is the olfactory and usually there is sufficient traction to partially disrupt this nerve Because it is richly vascularized it is better to coagulate and divide it at this stage to avoid troublesome bleeding during the operation or a postoperative hemorrhage. With further elevation of the frontal lobe the tumor becomes visible If the tumor is still confined to the sella, one or both optic nerves and the chiasm can be seen. At times there is a suprasellar extension of tumor which obscures the entire visual apparatus. When the tumor has been approached a cottonoid strip, to which a black silk stitch is tied, should be placed beyond the tumor to prevent blood escaping beneath the opposite frontal lobe This strip should not rest on the optic nerve.

The tumor is then aspirated (Fig. V–3) with a fine-bore sharp pointed needle attached by means of a short rubber tube to a 20-cc. Luer syringe to exclude an aneurysm and to determine if there is cystic fluid in the tumor Occasionally blood will be obtained from a pituitary tumor It may be the result of hemorrhage into a tumor or it may result from a very vascular adenoma It is advisable when blood is obtained on aspiration to watch the capsule of the tumor carefully to see if it immediately becomes tense again and to see if there are expansile pulsations It is advisable also to have a piece of temporal muscle a piece of gelfoam or both ready to patch the opening if it should prove to be an aneurysm

If the tumor is cystic the fluid should be aspirated to collapse the

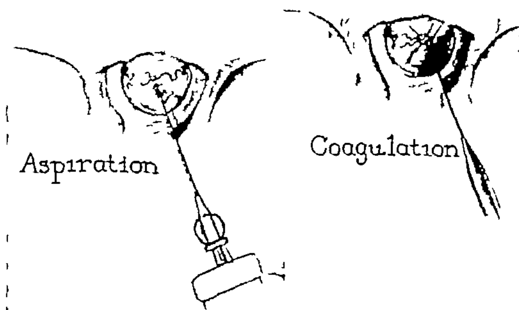


FIG V-3 See text In the drawing the rubber tube between needle and syringe is not shown. *The presence of a rubber tube provides better vision and affords the surgeon more freedom of movement, since the aspiration can be done by a nurse or an assistant while the surgeon holds the needle*

capsule and shrink it away from the nerves and chiasm It may be necessary to use a brain cannula if the fluid is of a thick consistency When the lesion is proved to be a neoplasm * the capsular vessels are coagulated (Fig. V-3) and then the capsule is incised in a cruciate fashion (Fig. V-4) and intracapsular removal is begun. A piece of tissue is taken for immediate fresh frozen section diagnosis (Fig. V-4) by the pathologist then the entire intracapsular portion of the tumor is removed by means of a small gallstone scoop curet, pituitary forceps and Gruenwald punch (Fig V-5) Often the adenomatous tissue can be removed by use of the sucker (Fig V-5) As the adenomatous tissue is removed, the capsule collapses and folds into the enlarged sella away from the nerves and chiasm. The capsule is gently teased free (Fig. V-6) and resected to the floor of the sella, thus removing all pressure from the visual apparatus A careful inspection is carried out in order to detect any parasellar extension If such is found it should be removed also Sometimes this tissue is found between the optic nerve and its corresponding internal carotid

* I usually start a transfusion of blood when the tumor is exposed and let it run in slowly—the patient receiving the last of the blood as the dressing is being applied or while reacting from the anesthetic in the postanesthesia or recovery room Five hundred cubic centimeters of blood are used for adults and 250 cc for children

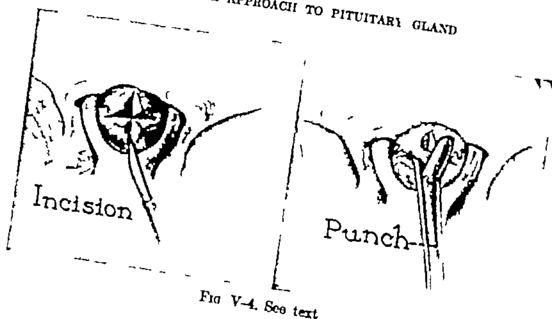


FIG V-4. See text

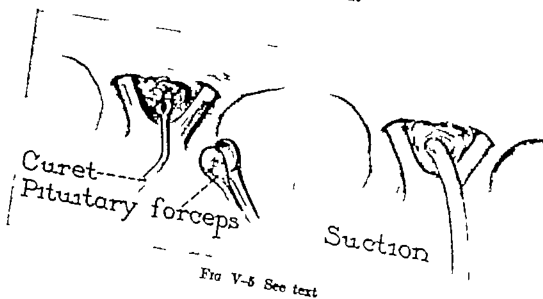


FIG V-5 See text

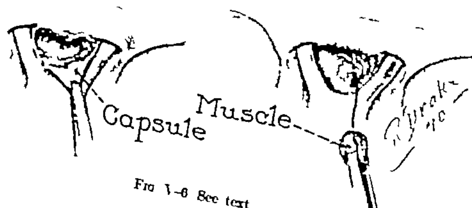


FIG V-6 See text

artery—sometimes lateral to the artery and rarely imbedded in the tip of the temporal lobe

It is advisable in most cases to leave a small pledget of muscle (Fig V-6) on the floor of the sella to minimize the danger of postoperative hemorrhage. The cerebrospinal fluid in the large syringe connected to the malleable needle in the lumbar region may now be replaced or it may be discarded. I usually send it to the laboratory for examination

No attempt is made to suture the dural incision along the sphenoid ridge and parallel to the falx. The edges fall back into juxtaposition and heal well If the approach has been transdural from the convexity of the frontal lobe the dura should be sutured with a continuous silk stitch

The bone flap is then inspected no decompression is made The edges of the flap are carefully waxed and the central portion of the pericranium and temporal muscle are stripped from the bone flap This minimizes bleeding from the bone and the danger of postoperative extradural clot In dealing with unusually vascular bone, occasionally the bone flap is stripped free of pericranium and muscle The edges of the skull and the bone flap are drilled in order that the flap may be anchored firmly in position by two stainless steel wires. Then the anchoring dural stitches applied at the time of elevating the bone flap are sutured to the galea around the skull edges and all oozing points on the exposed dura (over the convexity of the brain) are controlled by means of electrocoagulation and bits of gel foam The bone flap is then wired in position The pericranium, temporal muscle and temporal fascia are then closed in layers, a continuous stitch of fine chromic catgut being used. The anterior portion of the pericranium, which was so opened in the forehead region as to create a little flap for covering the anterior inferior perforator opening, is sutured before the posterior portion so that an accurate coverage is accomplished This likewise minimizes the risk of an unsightly depression in the forehead

The scalp flap is then replaced and the galea is sutured with a continuous stitch of fine chromic catgut. The skin is approximated with interrupted black silk Occasionally in children in order to shorten the operative procedure and the anesthetic, I have used a continuous silk stitch in the skin without any untoward development.

After the application of a gauze dressing held in place with a circular bandage of 2 inch gauze and adhesive tape the patient is transferred to the recovery room on a cart, to remain until he is out of anesthesia. Immediately in the recovery room the rectal temperature is obtained If the temperature is below normal extra blankets and hot water bottles are applied until a normal temperature is recorded. It has been my experience since first operating in an air conditioned operating room that most patients undergoing craniotomy will have a subnormal temperature immediately thereafter

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Questions and Answers

QUESTION At the time of operation, is there any danger of increasing the damage to the optic nerve which has been produced by the anterior cerebral artery?

DR. LOVE To be rather dogmatic, I would say no Still, there is always danger in operating for a pituitary tumor or any lesion in this area. I would judge that the questioner would like to know whether, in exposing the tumor and removing it, such a procedure would jeopardize the visual apparatus further as a result of pressure of the anterior cerebral artery on the optic nerve or chiasm. Of course, if the frontal lobe and the anterior portion of the circle of Willis are elevated to expose the visual apparatus and the tumor, then the groove can be seen very distinctly on the visual apparatus. I refer, of course, to the groove produced by the pulsating artery Now, *if that groove is detected and if discoloration and rather marked* compression of the visual apparatus also are seen, it is fairly clear that even though the pituitary tumor which lies below or even extends above the level of the visual apparatus may be removed successfully, the prognosis for return of the visual loss is not good It is true that if dissection and removal of the tumor are done with the usual care, in the presence of such a groove, the operation will not cause the vision to become worse Yet we must realize that in the presence of the groove the prognosis cannot be as good as it would be if the grooving process caused by arterial compression were not present.

QUESTION What is your opinion regarding x ray therapy in the treatment of pituitary tumors as expressed by Dr Horrax in a following chapter?

DR. LOVE I was extremely interested in the fine presentation and neurosurgeons generally would be spared much trouble if they could duplicate the results that he has shown so beautifully Several aspects of this matter give me considerable concern For instance, there is a group of patients—about 20 I think—in whom there was *no visual loss* It would be difficult for me to evaluate the result of any type of therapy in that group of patients And I think I would hesitate to advise any therapy for the patients with an enlarged *sella turcica* and also mild symptoms

referable to the pituitary without any visual loss For instance, I should hesitate to advise roentgen ray therapy, and I certainly would not advise surgical intervention in such a case What disquiets me is that on more than one occasion I have encountered a patient who has received what would be considered adequate radiation therapy but who nevertheless continues to sustain losses in vision and experiences considerable headache I emphasized, the other day, that I personally do not consider headache as a prominent symptom in the average patient who has a chromophobe tumor On occasion I have done surgical exploration (without beneficial effects) for such patients, who have received what has been called "adequate therapy" by radiotherapists In such instances, much to my surprise, when the sella turcica is exposed I have found a few strands of fibrous tissue, but no mass lesion whatever, and the nerves are atrophic The patient obtained no benefit, so far as his vision was concerned, and I should be the first to hasten to suggest that in one case the patient probably should be classed with the group to which Dr Horrax referred as 'improperly treated' In this case the bone was devitalized it did not heal and the bone flap had to be removed The roentgenologic effect was very marked

I also recall a woman from a neighboring country who came to us with the symptoms and signs, ophthalmologically, roentgenographically and otherwise, of a pituitary tumor At the time of operation we found a cystic lesion of the sella turcica which was causing marked compression of the optic nerves and chiasm. The contents of the cyst were evacuated they proved to be clear fluid, with a low protein content. The cyst was removed and submitted to the pathologist, it proved to be only a simple fibrous cyst After removal of the tumor the woman's menstrual periods were restored. She went home, became pregnant and gave birth to a normal child Moreover her visual loss was restored or at least her vision was restored to normal.

I question if we should treat the chromophobe adenoma with roentgen rays I would omit chromophile tumors from such questioning for I will agree with anybody that roentgen ray therapy is the procedure of choice for this type of tumor but fortunately only about 5% or less of the chromophile lesions ever come to operation because of compression of the visual apparatus

I have had the pleasure of seeing one of Cushing's famous patients I did not know this until after I had told her that she had acromegaly and that she did not need any treatment because she was doing very well She said Thank you very much Dr Cushing told me that about 20 years ago Well we have all seen the acromegalic patient do very well with radiation therapy The symptoms of endocrine hyperfunction abate under

such therapy But I would restrict my remarks principally to the chromophobe adenomas I question whether radiation therapy directed to the sella turcica with sufficient intensity to destroy a chromophobe adenoma of the pituitary would not *also destroy or severely* impair the function of the remaining pituitary gland I think one of the greatest satisfactions a neurosurgeon ever experiences is to operate upon a woman for a chromophobe adenoma, to remove the tumor and then to learn that the patient's menstrual cycle has become normal again, so that subsequently she gives birth to a child We might even recall the apt remark that "maternity is a matter of fact, paternity is a matter of opinion"

Dr. Love Several men have asked about the sponge which I recommended for closure of the frontal sinus when that structure is inadvertently or purposely opened. It is known as ivalon sponge, it is a plastic material I went down to the drugstore this morning to see if I could buy one, but I was not successful. Still, I understand that the sponge can be bought at any ten cent store women use it for cleaning in place of a sea sponge or a rubber sponge. We learned about this sponge from our associates in the sections of general and vascular surgery It can be sterilized in the autoclave it can be cut into any size of sheet or any thickness that may be needed. The reason it is so satisfactory is that the fibroblasts grow into the interstices of the sponge and produce very firm closure of any defect which you may wish to close. If ivalon material is placed around the aorta or about an aneurysm for instance it constricts the vessel as the fibrous tissue grows into the sponge I would not recommend it for the enclosure of intracranial aneurysms because it stimulates the production of fibroblasts and scar tissue. I have however, used it intracranially We reported one case in which we employed this material to close a fistula after complete removal of a tumor of the cerebellopontine angle. However, if this material is used to close a cerebrospinal fluid fistula, the fluid may continue to leak for 6 or 8 days afterward, because the sponge obviously cannot be a solid barrier As I have said the purpose of the sponge is to provide a substance into which scar tissue will grow, and that is why we use it. We have used it to close defects in the frontal sinus and other openings

Question Do you ever feel that the anterior cerebral artery should be divided because of the compression on the optic nerve?

Dr. Love No, I have never deliberately clipped and divided the anterior cerebral artery to remove the tumor in question On more than one occasion I have applied silver clips and then divided the anterior communicating artery to allow retraction of the circle of Willis laterally for proper exposure of the tumor

CHAPTER VI

The Surgical and Irradiation Treatment of Pituitary Adenomas

GILBERT HORRAX, M D

During the last decade of the nineteenth century the clinical diagnosis of pituitary tumors became established, and soon thereafter (1 2) intra cranial surgical procedures were attempted for the removal of these growths The *excessive mortality of these early intracranial operations* led to a search for less hazardous methods of approach to the sella turcica, and thus the transphenoidal operation was developed and perfected by Schloffer (3), Kanavel (4) Hirsch (5) Halstead (6), and Cushing (7) In these early days, surgery was the only known method of attacking pituitary tumors and the transphenoidal approach was utilized with considerable success and eventually with a relatively low mortality until the late 1920 s Since then with the advent of modern neurosurgical techniques and various helpful adjuncts, the intracranial operation for the exposure and removal of pituitary tumors has been the procedure of choice by practically all neurosurgeons and it was shown by Henderson (8) in reviewing Cushing s entire series in 1939 that this method combined with postoperative radiation gave the highest percentage of good results I have discussed elsewhere (9) the reason for the somewhat higher present day mortality of the intracranial operation compared with the transphenoidal procedure This is due solely to the radical operations on large intracranial extensions of adenomas many of which can be salvaged by heroic measures only

The treatment of pituitary tumors by means of deep roentgen therapy was first attempted by Béclère (10) and Gramegna (11) and Béclère reported 13 years later that the patient he had treated in 1909 was in excellent health It was 4 years after this report by Béclère that the first fairly large series of patients with pituitary lesions treated by radiation was reported by Heinismann and Czerny (12) These authors collected 73 cases from the literature and added 15 of their own. In general they felt that the best results had been obtained in patients with acromegaly although some of the patients with presumed chromophobe adenomas were benefited. However no mention was made as to the length of time that patients had maintained their improvement

From this time onward many reports concerning radiation treatment for pituitary adenomas have appeared As early as 1925 Bailey (13) and

Frazier and Grant (14) felt that a trial of radiation should be given to patients with only slight visual disturbance, and this attitude was likewise advocated with some misgivings by Dott (15) in 1927 Towne (16) in 1930 was the first neurosurgeon to show any real enthusiasm for radiation versus surgery in the treatment of pituitary adenomas He concluded as follows 'It is proposed that all pituitary adenomas be treated by roentgen ray under the observation of the ophthalmologist and the neurosurgeon, that the treatment be stopped as soon as improvement begins, and that surgery be undertaken short of 6 months only when visual acuity and fields recede under roentgen ray therapy Towne reported 5 patients, 3 of whom had their vision restored for considerable periods—one for 5 years, one for 2 years, 8 months, and one for 2 years, 10 months However, 2 of these patients had recurrences and were not relieved by further radiation

This report by Towne was little more than "a voice crying in the wilderness," as an article by Frazier (17) in the same year dampened any prospects for good results to be expected from roentgen treatment In reviewing his series of chiasmal lesions, among which there were 129 pituitary adenomas, he stated that only one patient had had any sustained benefit from radiation. He did not say how many patients had been given this treatment.

Frazier's attitude as to surgery versus radiation for pituitary tumors may be said to have been the general feeling of most neurosurgeons at that time and was reflected in similar reports by Cairns (18), in 1935 and by Rand and Taylor (19) in the same year All, however, agreed that patients suffering from acromegaly were more likely to be benefited than were those having chromophobe adenomas. The neurosurgical point of view continued in spite of favorable reports by roentgenologists, such as that of Pfahler and Spackman (20) in 1931 but this report dealt in generalities only without giving any end results.

What seemed at the time to be the lethal blow to radiation for pituitary tumors was delivered by Cushing (21) in 1932 when he said 'So far as concerns radiotherapeusis at least in the case of chromophobe adenomas it is safe to say that it will come to be discarded just as radiation for exophthalmic goiter has been so soon as neurosurgeons as a class perfect themselves in the details of the operative procedure" In extenuation of this remark it may be said that certainly up to that time radiation therapy for pituitary tumors had shown extremely inconsistent results to say the least and in not a few instances patients had had irreversible damage to their optic nerves while undergoing radiotherapy and neurosurgeons were obviously averse to taking any chances of this kind since the good results obtained by surgical removal had long been established.

This, then, was the general attitude in respect to the treatment of pituitary adenomas until about the middle nineteen thirties, namely, that in cases in which vision was slightly to moderately affected, a trial of radiation therapy was warranted, but if improvement did not take place within 4 to 6 weeks, or if vision became significantly worse at any time during such treatment then prompt operation was advised From about the year 1938 onward there began to appear more hopeful reports on the radiation treatment of pituitary adenomas In 1939 Henderson (8) reviewed Cushing's large series of these tumors in a comprehensive monograph. He showed conclusively that when patients with adenomas had been given x ray therapy after operation, the prolonged results were distinctly better than when operation without radiation had been employed. Even before Henderson's review Sosman (22) in 1937 had stated that his results " indicate that satisfactory remission of symptoms and signs will be obtained in over 50 per cent of patients with chromophobe adenomas, in 90 per cent of the chromophile adenomas and in the majority of basophile adenomas" This same attitude was again expressed by Sosman (23) in 1939 at which time there had been a longer follow up period for his patients In this paper he likewise put forward the belief that radiation results would continue to be better with further refinements of technique and larger doses delivered to the growth This prediction has been abundantly confirmed. Further support of radiation therapy was offered by Davidoff and Feiring (24) in 1948 Of a total of 88 patients with either chromophobe or chromophile adenomas treated only by radiation 43 or 48 per cent were either improved or their vision held at a useful level On the other hand, even up to this time the general neurosurgical attitude toward radiotherapy was still very much the same as it had been during the previous 10 years. Thus in a paper written in 1948 Grant (25) says If the visual acuity is better than 6/9 in each eye and if the atrophy of the optic nerve is not advanced irradiation therapy is indicated regardless of changes in the visual fields or sella.

Our own attitude as to the advisability or indication for roentgen treatment of pituitary adenomas was very much like the views expressed by Grant until the year 1950 when we began to treat these tumors with the 2 million volt apparatus at Massachusetts Institute of Technology using the rotational method and delivering a tumor dose of 4000 r Previous to that time we had used the standard 200-kv machine and usually an 1800-r dose was delivered to the tumor through bilateral temporal ports At times this dose was repeated once or twice at varying intervals if progress was not as satisfactory as we thought it should be and if vision did not deteriorate greatly or rapidly

The main purpose of this paper therefore is to compare the results ob-

tained in the treatment of pituitary adenomas, particularly as to the efficacy of roentgen therapy as utilized in the ways and in the amounts just described The comparison to be made is between that period from 1932 to 1949 inclusive, when smaller amounts of radiation were delivered to the adenomas by the 200-kv machine, and the period from 1950 through 1955 when we have utilized a higher tumor dose by means of rotational therapy with the 2 million volt apparatus I have not tried to collect large series of cases from various clinics where differing methods both as to surgery and radiation therapy might have been employed and from which any comparisons would be either difficult or impossible The patients whose treatment is to be described here were either operated upon by a similar method or were given their radiation by a single group in a uniform manner It would thus seem that a fair estimate could be made as to the results obtained during the 2 periods with which we have been concerned It is recognized at once, however, that for the patients who have been treated since 1950 a follow up course of only 1 to 5 years is available, and it is conceivable that after a longer interval the end results may have to be re-evaluated.

In the statistics and discussion which follow it should be understood clearly that only chromophobe and chromophile pituitary adenomas are considered. The basophilic adenomas are too few in number and their problems are different and such suprasellar tumors as craniopharyngiomas, meningiomas and other rare growths in this region are rarely if ever radiosensitive

For the purpose of over-all statistics it may be said that our material consists of a total of 335 pituitary adenomas which have been so diagnosed at the Lahey Clinic from 1932 to 1955 inclusive Of this number, 141 have been verified pathologically whereas in the remaining 194 the diagnosis has been made by the finding in all cases of a large ballooned out sella in the x-ray together with other pituitary stigmata such as optic atrophy, visual field defects and so forth (Table 1)

In previous papers with various collaborators (26, 27), I have set forth our experience with certain aspects of our treatment of pituitary adenomas either by surgery or radiation or by a combination of the two both before and after the period when we have had access to the 2 million volt apparatus

In the earlier period 173 patients were treated by radiation only, or were operated upon because radiation had not improved their condition Of the total number there were 74 who were treated in the hope of benefiting certain endocrine disturbances The remaining 99 were treated for visual loss or such symptoms as intractable headache especially in acromegalics These 99 therefore, are the only ones for whom there would ever have been

TABLE 1

Pituitary Adenomas

Verified pathologically	
Chromophobe	122
Chromophile	19
Total	141
Verified by x-ray, etc.	
Chromophobe	140
Chromophile	54
Total	194
Grand total	335

any indication for surgery, so that it is from this number that figures must be drawn as to the necessity of an operation when radiation failed. There were 58 of these 99 patients or 58.5 per cent who were operated upon because radiation in the amounts they had received had failed in that their vision deteriorated or was not held at a useful level (Table 2).

In other words, in this period from 1932 to 1949 inclusive, in addition to a fairly large group of patients, 46 in all, who were operated upon because of poor vision before any radiation was given to them, subsequent operation was considered necessary on nearly 60 per cent of the 99 patients in whom a previous trial of radiation therapy had been made. This figure should be compared with that which is to be given for the period of 1950 to 1955 inclusive.

So far as the end results for this group of patients is concerned, we have the following data. Five of the 58 patients operated upon died following operation. Three showed no improvement for periods of 1, 2 and 7 years and it has been impossible to obtain follow-up information in 4 instances.

The remaining 46 patients have been followed from a few months up to 21 years for an average of 7½ years. It is known that 39 of these patients

TABLE 2

Results of Roentgen Treatment 1932–1949 Inclusive

Radiation only, or surgery because radiation not effective	173
Subtract patients without visual loss	74
Total	99
Operated upon because radiation not effective	58 (58.5%)

TABLE 3
Results of Roentgen Treatment 1950–1955 Inclusive

Total patients treated with 2-million volt apparatus	95
Subtract patients without visual loss	29
Total	*66*
Operated upon because radiation not effective	8 (12.1%)

maintained their improvement for 4 years or more, and that 16 maintained their improvement for over 10 years. Two of the 39 died, one after 7 years, the other after 10 years

From the year 1950 to the present time our Department of Radiology has treated nearly all of the pituitary adenomas which have been so diagnosed at the clinic. Out of the total 106 patients in this period, 11 were operated upon before radiation because it was thought that their vision was so greatly impaired it would be unwise not to give them prompt operative relief from pressure on the optic nerves * Of the remaining 95 there were 66 *who had some degree of visual impairment* or intractable headaches Only 8 or 12 1 per cent of these 66 patients have so far had to be operated upon because of the failure of radiation (Table 3)

When this figure of 12 1 per cent is compared with the 58.5 per cent of patients who had to be operated upon in the earlier period, it is obvious that a substantial gain has been made in the results to be expected from radiation in the treatment of pituitary adenomas Incidentally, this figure of 12 1 per cent is even distinctly better than the figure of 18 4 per cent which we reported previously when statistics through the year 1953 were available Furthermore, as mentioned in this previous report, 2 of the patients operated on were shown to have no pressure whatever of the adenoma on the optic nerves. In one of these patients vision returned to normal and in the other it remained stationary but it was clear that the operation could not be given the credit for this.

As to the end results for patients treated from 1950 to 1955 inclusive, it is of course obvious that only 1 to 6 years have elapsed since their treatment was instituted and that a longer period will be necessary for final conclusions Up to the present, however we feel there is every reason for encouragement because such a small percentage of patients have had to be operated upon.

DISCUSSION

From a review of the treatment in this series of patients having pituitary adenomas it would seem unmistakenly evident that neurosurgeons in gen

* Two of these patients were operated upon solely for the control of cerebrospinal rhinorrhea which was the reason for their admission.

eral must revise their thinking in respect to surgery versus radiation in the treatment of these lesions In our experience, even when vision is considerably impaired, in some instances as low as 20/50 with one eye and even lower with the other, a careful trial of radiation, preferably with the 2 million volt apparatus using the rotational method, is indicated. We have learned, too, that vision may become somewhat more disturbed for several days or possibly a week or two during the course of treatment but will eventually improve However, if there is rapid or serious visual failure, operation should be undertaken promptly

Certain other aspects of the situation concerned with radiation therapy should be noted. We have never seen any ill effects of radiation on any brain function nor the development of cataracts resulting from this type of therapy Likewise the use of the x ray does not make subsequent surgery more difficult

It has been said that approximately 20 per cent of pituitary adenomas are cystic and therefore would not be affected by radiation. Our figures would by no means bear this out since during the past 6 years radiation has benefited some 90 per cent of our patients In only 1 of the 8 patients operated upon was a cystic tumor found

In his article in 1937 Sosman stated "It might be more valuable to analyze and compare failures rather than to consider only good results A brief word therefore may be in order as to our 8 patients upon whom we felt it was necessary to operate because of the apparent failure of radiation therapy In every case vision had declined so greatly that surgical relief of pressure on the optic nerves seemed urgently indicated

One patient had a huge intracranial extention of her adenoma in one the tumor was largely cystic in a third nothing was found in the sella except a collection of colorless cerebrospinal fluid and in a fourth the growth was extremely firm and fibrous One patient had had sudden hemorrhage

TABLE 4
Patients Operated upon 1950–1955 Inclusive After Receiving 2 Million Volt Therapy

Operative Findings	Result
1 Huge intracranial extension	No improvement
2. Sella filled with cerebrospinal fluid	No improvement
3 Cystic tumor	Improved
4 Fibrous tumor	Great improvement
5 Soft adenoma	Normal vision
6 Soft adenoma	Improved
7 Soft adenoma	Improved
8 Hemorrhage in adenoma	Died

into the adenoma and one had a convulsion following a head injury There were no unusual features in the remaining 3 patients although in one of them, as mentioned before, the adenoma sunk away from the nerves and was exerting no pressure on them, and she recovered normal vision subsequently Of the 8 patients, 5 improved greatly, in 2 vision was unchanged, and one patient died (Table 4)

SUMMARY

The history of the treatment of pituitary adenomas both by surgery and by radiation, or a combination of the two has been reviewed briefly

Although surgery at times is brilliantly successful, it carries a distinct hazard, especially in cases with a large intracranial extension of the adenoma. Surgery is indicated in patients whose vision is seriously impaired, or if vision has failed rapidly presumably from hemorrhage into the tumor

In all other patients having the usual criteria of a pituitary adenoma, either chromophobe or chromophile, a trial of radiation therapy is indicated before surgery is considered. Even if vision declines somewhat during the course of such therapy, careful observation of the visual fields and acuity will nearly always show eventual improvement

In our experience a total dose of 4000 r delivered to the tumor is the optimum. When given by the 2-million volt apparatus using the rotational method there seems to be less clinical reaction, no permanent depilation and no dermal difficulties. Utilizing this method, only 12 1 per cent of our patients have thus far had to be operated upon during the last 6 years

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Questions and Answers

Question What is your opinion regarding x ray therapy in the treatment of pituitary tumors as expressed by Dr Horrax?

Dr. Penfield From my own experience there have been a certain number of patients treated by radiation whose headaches were not relieved and in whom we postponed operation much too long and left them with years of suffering. I can remember at least 2 chromophile adenomas with acromegaly whose headaches were never relieved by x ray therapy Not everyone has the great and enviable advantage of living in Boston and not everyone is as close to the Massachusetts Institute of Technology

and the 2 million volt machine. I would like to ask Dr Horrax, should we take the same attitude and draw the same conclusion in regard to radiation therapy that he has drawn, or is that a horse of another color?

QUESTION What causes the headache in patients with pituitary tumors?

DR. PENFIELD I used to think I knew I always described such head aches as the bitemporal sort of pressing headache due to the tension within the sella. But as time has passed, I am not so sure. Occasionally you see the intractable headache, even with x ray treatment, and yet sometimes there is nothing to cause tension within the sella turcica I don't know what it is

QUESTION I should like to ask Dr Penfield if, in his experience, head ache is a more prominent symptom of one tumor than of another? For instance, is headache more common in the presence of the chromophile or the chromophobe type of adenoma?

DR. PENFIELD I can't answer that, my experience is not sufficient.

QUESTION What is your opinion of headaches in patients with pituitary tumors?

DR. HORRAX I agree with Dr Ray that in our experience the acromegalics are the ones who complain most bitterly of headache, and it's a curious thing to me that in my experience headaches of that type are more benefited by x ray than they are by surgery—not always, but in the vast majority of cases. Someone also asked about the further deterioration of vision after operation. Of course that certainly can happen. We can all recall cases of that kind

I vividly recall a well known executive who was operated on by Dr Cushing once or twice by the transphenoidal method He then had some x ray treatment but didn t do very well, probably from insufficient x-ray treatment Dr Cushing next did a craniotomy on him. He removed the tumor but the vision kept going downhill until the patient was nearly blind in one eye and vision was considerably impaired in the other Further x ray treatment was given but this was in the earlier days before the 2-million volt machine This patient was not benefited so I operated on him There were many adhesions from the previous operations. A large adenoma was found which was adherent to the optic nerve In carefully teasing the capsule away from the good optic nerve there was evidently some further damage He was already blind in one eye and as a result of the operation became blind in the other This man did perfectly well otherwise and returned to his executive job This is the sort of thing that can happen when there have been previous operations I do not believe the x ray treatment had anything to do with the adhesions around his chiasm

Dr Penfield asked about the type of x ray machine As I have said before, you can get in 4000 r (which we believe is the optimum dose), by using

the 200-kv machine. Dr. Smedal, our roentgenologist, and others have assured me that this is true. I think that this same question was put to me in Montreal one time when I was up there talking about this same subject. On the other hand, if you give 4000 r with the 200-kv apparatus you are likely to get depilation over the temporal areas which may not be very important in women because they can camouflage it, but you may also get a very marked dermatitis. The value of the 2-million volt machine with rotational therapy, where the patient is rotated and gets the treatment through various ports, is that you can get in an adequate dose without these side effects.

Dr. Love said he would not treat people who do not show visual disturbances. I thought I made it clear that I have eliminated those cases from the statistics which I showed you. Those patients would not have any operative indication. I am comparing only the patients with visual disturbances. I may say a great many of our acromegalics, in addition to the intractable headaches, did have some form of visual disturbance. The patients without visual disturbance were given x ray treatment because of other pituitary or endocrine abnormalities and do not enter into this picture in so far as surgery versus x ray is concerned because they would not come to surgery in any case."

QUESTION: Well, now I think there is some question about what you mean by sufficient visual impairment, whether it is acuity or fields, or what.

DR. HORRAX: All I can say is this—we followed these patients at least once a week during the time of their treatment. This takes about three weeks as we give a relatively small dose at a sitting. We found there was less danger of hemorrhage into the adenoma when they were treated in this manner. After the treatment we follow them along at frequent intervals, and have followed nearly all the patients during this last 5 years. What we mean by adequate improvement is that they have either a normal visual acuity or adequate visual acuity to be able to get around and do their type of work or be useful—useful vision in other words. Now that may not mean that all of them improved to complete restoration of their visual fields and 20/20 vision but they do have adequate useful vision. As I say this is only over 5 year period and it may be that some of these people whom I talk to you about today may come to operation at some time. However, the point is this—I think if you look up the statistics you will find that your mortality in pituitary lesions is a little higher than you think—especially in patients who have rather large intracranial extensions where you have to pull the adenoma out from behind the chiasm and so on. With the ordinary type of adenomas which form the majority of patients the mortality is somewhere between 2 and 4 per cent. This has been true in our series and in Jefferson's series in England. It is also true of Olivecrona's series; however, with large intracranial extensions the mortality is much

higher In those cases, surgery is almost always indicated because it is the only way you can salvage some of them On the other hand, we are trying to get away from even that 2 or 3 per cent mortality because, although it is low, if you happen to be one of the people who falls into that category, even a low mortality rate cannot be overlooked That's why we are stressing this x ray treatment so much

QUESTION Did you say that a satisfactory result from x-ray treatment is one in which there is no further visual loss or improvement?

DR. HORRAX Provided the vision which they had to start with was useful vision.

QUESTION How long would you continue x ray therapy or wait before starting surgery, if the vision did not improve or become progressively worse?

DR. HORRAX If during the course of the x ray treatment or within the subsequent few weeks or months vision keeps on deteriorating, we occasionally give a second x ray series However, operation is performed if vision cannot be held at a useful level, or if vision deteriorates very rapidly —which may be an indication that something like a hemorrhage into the adenoma occurred, making surgery mandatory However I have seen a number of patients who have some deterioration during their treatment, but then gradually begin to improve until they eventually got back useful vision

QUESTION Then there are no definite standards to be used—it's when you feel that visual loss has actually come to the point where you might not have useful vision?

DR. HORRAX That is right

QUESTION Will you comment further upon repeated series of x ray treatments if symptoms return?

DR. HORRAX If the patient has lost further vision 6 months or more after radiation, should he be returned to the roentgenologist? I would make such a recommendation—unless vision deteriorated very greatly If gradual deterioration took place and vision was still useful in one eye, I would cautiously try one more series of x ray treatment We have had to do that with fewer than half-a-dozen patients But, of course if vision deteriorated further you would have to operate and naturally personal judgement comes into this All patients must be followed very carefully over long periods of time by the roentgenologist the ophthalmologist and the neurosurgeons because as I have said before very careful follow up study from many standpoints is necessary

QUESTION TO DR. RAY Do you agree with Dr Horrax?

DR. RAY I would agree with Dr Horrax as he has outlined it However one thing worries me When the emphasis is put on x ray therapy for pituitary tumor and surgery is turned down, later it may become a belief

that these tumors are no longer a neurosurgical problem. Then people who should not be treating these cases will start treating them and they may forget to follow the eye fields The other thing that is a cause for concern is the frequency with which the diagnosis may be in error I know it can happen, and it can happen to the best of us What may appear to be a chromophobe adenoma may actually not be that at all, and it is a mistake then to treat the patient with x ray and delay the time of operation.

DR. LOVE I would not say that I agree entirely with Dr Ray I have in mind a patient who has been treated in our own institution, and whose condition has been followed, he was treated for what was thought to be a chromophobe adenoma of the pituitary body He returned with a very marked loss of vision After examining him I told him that immediate operation was imperative although he had returned with the idea that he would simply receive more roentgen ray treatment He accepted operation and at surgical exposure I found one of the largest intrasellar and suprasellar epidermoid lesions I have ever seen. You might say it extended everywhere—in the frontal lobe, all about the visual apparatus, and in nearly every other direction Now, this man obtained marked recovery of visual loss within a very short time, and he is one of the happiest men I know

There have been other and comparable patients Two patients had been treated elsewhere with roentgen rays for 'pituitary tumor," but actually neither of them had a pituitary tumor We have seen a number of such patients. I would heartily agree with Dr Ray that the diagnosis is not always perfectly clear and most of us are frank to indicate this in our talks and writings As you all know, Dr Horrax has pointed out very beautifully how important it is in treating another type of intracranial tumor to remove completely the cerebellopontine angle tumor If subtotal removal only is done in the hope of thereby lessening mortality rates, morbidity rates very often increase and a second operation may involve higher mortality rates. I am afraid that if this method of treatment of chromophobe adenomas (meaning irradiation) becomes generally favored many chromophobe adenomas of the pituitary body are going to steal like a thief in the night behind the chiasm and secure themselves under the optic nerves in the parasellar area and out into the temporal lobe If that happens we may expect the mortality rate to increase tremendously—perhaps to as high as 60 or 70%—when operation is finally attempted. By contrast if you have a patient with bitemporal hemianopsia and a suspected tumor which does not seem to have parasellar extension but who does not have central scotomas to indicate severe damage of the optic nerves then certainly, as Dr Horrax has indicated the risk between operation and no operation is very low After operation restoration of vision is so rapid that I think it most important not to lose sight of the period in

which operability and curability are most likely to be obtained, even though other methods admittedly are associated with less risk to the patient.

DR. HORRAX If I may make a comment, I am sure Dr Love is right as to hesitancy regarding radiation, and as a matter of fact, that was exactly my attitude toward this whole situation before we started this newer type of therapy, however since then I have had to become optimistic about it, because we have apparently had such good results so far I want to reiterate then—we follow these patients very carefully, so that we hope we can recognize signs of deterioration early Now as to the mistakes in diagnosis, I am sure we have all made them occasionally and some of the patients we have reported may not have pituitary adenomas On the other hand they are doing well so far If we find that there is any reasonable doubt as to the diagnosis we do either an arteriogram, encephalogram, or ventriculogram to see if there is anything such as the epidermoid that Dr Love spoke about, and we have had occasional ones such as that I think you must turn every stone in all those patients to be sure that your diagnosis is right if there is any doubt In the vast majority of them I am sure there is very little doubt

QUESTION Can radiologists throughout the country still treat pituitary tumor without the 2 million volt machine?

DR. HORRAX Yes, that is, if the roentgenologist can get in an adequate amount. But the difficulty is that it usually involves depilation and possibly skin difficulties.

QUESTION Is Cortisone combined with x ray therapy at the Lahey Clinic? How many x-ray treatments are given over what periods of time?

DR. HORRAX We feel that cortisone is indicated if there is some general indication for it from the endocrinological standpoint and, of course, there are many people either those having x ray treatment or otherwise, who will profit by cortisone Certainly, if a patient has to be operated on we almost always administer ACTH or cortisone both before and after operation. Sometimes we have seen patients whom we thought had not improved enough after x ray therapy who were improved both as to their endocrinological status and their vision after they were given a course of cortisone They improved so much on cortisone that it was not necessary to do any further studies on them to determine if they had a possible intracranial extension or whether the pituitary adenoma was in such condition that operation was required As to further x-ray treatment I commented before that we have had to suggest to a few patients a second series of treatment after several months or even longer but that has been very rarely Subsequent treatment takes about three weeks with the 2 million volt machine using rotational therapy

QUESTION Using the 2 million volt x ray machine in destroying the

pituitary, is it likely that these patients must be continued on Cortisone therapy, whereas those who are dealt with surgically might get by without it

DR. HORRAX You do not destroy the pituitary by this machine by this dosage at all, I think you simply destroy the adenoma or shrink it in some way As far as I know there has been no indication to use cortisone for replacement therapy because of any damage to the pituitary itself which is very resistant to the roentgen ray It's just the adenoma that is destroyed.

QUESTION TO THE PANEL Have any members of the panel had the experience of exploring and finding an empty pituitary fossa after roentgen therapy?

DR. LOVE I was about to say that I have, and in fact I have already mentioned it

DR. RAY I can't recall.

DR. HORRAX The patient in whom I found this empty sella turcica must have had some pituitary left because she had no particular or outstanding pituitary deficit. In her case it was simply a loss of vision which we assumed was due to an adenoma and we do not know that there were fragments of adenoma left there But, certainly just letting the fluid out did not affect her vision one way or the other

QUESTION TO DR. HORRAX Then we can be assured that hypophysectomy cannot be effected through any method with your betatron?

DR. HORRAX Not with the dosages that we believe are adequate

QUESTION Is the use of air studies helpful in determining the surgical indications of pituitary lesions and whether they are improving or regressing.

DR. HORRAX If we feel there is any real doubt as to the diagnosis of a pituitary adenoma or suspect some other type of parasellar lesion we conduct diagnostic studies We prefer arteriograms or encephalograms but occasionally perform ventriculograms If there is evidence of further progress of the lesion any of the above studies may be done I think that here again it is simply a matter of judgement as to how far it is necessary to go and I feel that we must all be a little bit careful in doing these procedures Even encephalograms and ventriculograms carry a slight hazard and they should not be taken lightly One should not subject a patient to an unnecessary procedure On the other hand, if they do appear to be indicated then there is no contraindication to doing them.

Now if I may say from my standpoint a final word on this I realize perfectly well that this is a very controversial subject and it possibly should not even be brought up at this present stage of our knowledge but I would add simply that I had a very skeptical attitude about x ray treatment just as Dr Love did some 5 or 6 years ago It was only when I began to look up our statistics after we started using this 2 million volt machine

that I realized what astoundingly good results we had I then thought I should see what we had accomplished in the past and what we were accomplishing during this newer period I was really astounded to find out how good these results had been and I simply pass them on The whole thing, as I am sure you know, is a matter of mature judgment plus following your cases for long periods This is really all I have to say and I apologize for bringing up such a controversial subject

QUESTION TO THE PANEL Do you agree with Dr Horrax concerning air studies as diagnostic tests?

DR. LOVE I have no desire to become known as "The Great Dissenter," yet it is a fact that over the years encephalography in the diagnosis of chromophobe adenomas of the pituitary body and even in the detection of small craniopharyngiomas or adamantinomas has not been a great help to me Personally, I would much rather rely on my estimation of the patient's clinical course and upon the judgment of my associates in ophthalmology as to the status of the vision I have seen a number of patients over the years who underwent air studies with results that were considered to be negative, as were results of angiograms yet they had progressive visual loss as demonstrated by Dr Rucker and his associates. In such instances I have had no hesitancy whatever in operating, and I have found space-occupying lesions which would account for the visual loss. I share Dr Horrax s view that any procedure, however simple, is associated with risk. You all know that occasionally a patient dies after a hypodermic injection. Well suppose you propose to anesthetize a patient and make an encephalogram but you then consider that the patient does not have choked optic disks, and conclude that shaving the head making a couple of bur holes for ventriculography are not warranted The only method left is angiography I think all three of these procedures at times will fail in helping you establish the diagnosis of an intrasellar lesion which is producing pressure on the visual apparatus.

DR. RAY I don t agree with that. We rarely resort to air studies but we have used angiography rather frequently of late mostly to find out what we could learn from it The distortion can usually be demonstrated but I am not sure that it adds materially to the diagnosis or to the plan of decision about operation.

QUESTION What is your opinion regarding the deleterious effects and changes to the brain resulting from radiation therapy?

DR. RAY It is true that in the series I discussed I alluded to one patient who had received large amounts of betatron It was given in an effort to destroy the pituitary (which is quite another matter from that which Dr Horrax has been reporting) This patient showed progressive deterioration and when she died autopsy revealed extensive changes in the brain due to irradiation.

We also have in print at the moment though not published, the account of 2 achromegalic patients who developed all the signs and symptoms of brain tumor and at operation, looked as though they had glioblastomas In each case, these changes were the results of repeated doses of x ray treatment over a period of years. One can easily point out that the mistake was in giving all the x ray, but in each case the series was given by someone who thought he knew what was appropriate In each case I think the dosage totalled somewhere around 10,000 r over a period of years Dr Browder operated on one of these patients and I operated on the other

Dr Horrax has already said what the dosage should be and I hope he will say, when he has a chance to discuss this what he feels about repeated doses of x ray I would also like to ask him what attitude he takes when there is no improvement in vision—if he assumes that it is a failure or is he content to accept it as all one can accomplish in the treatment of this patient? I have a purpose in asking this question because I think I have enough experience to lead me to believe that many patients whose vision is not improved by x ray subsequently get a very striking improvement from operation. Also I think that what is one man's opinion of dangerous progression of the tumor, is not what the opinion of another man would be Some might regard loss of vision to 20/50—or even up to 20/100—as still within the safe range of trying x ray treatment. I would be alarmed at that much loss of vision and I am frank to say that I am much more enthusiastic about operation than I am about x ray It seems to me that in the last few years with very few exceptions the patients who have been coming to me for operation have already had the limit of treatment by x ray I have never used the argument however that x ray treatment makes subsequent operation worse I do not believe that is the case at all.

QUESTION Comment on the mechanism of headache in pituitary tumors and its relationship to the various types of adenomas.

DR. RAY I agree with what Dr Penfield has said. I don t think we know for sure why a patient with a pituitary adenoma has headaches It can easily be reasoned that there are pain sensory structures in the area. The diaphragma sella is painful and the carotid which lies immediately adjacent is very sensitive to pain At least those structures might give rise to headache I think that probably all or many of us have seen patients with hemorrhage into an adenoma when there is an acute type of headache which leaves very little doubt that it is associated with that episode I suspect that in the majority of patients with pituitary tumors the headache exists on some other mechanism and I won t try to explain what The acromegalics were much more inclined to complain

of headache than the chromophobe types One might explain that the headache is in keeping with other pains which occur in the body, probably due to somatic overgrowth partially involving the periosteum and other pain sensitive tissues One has to be very cautious in anticipating benefit from an operation in a patient with any type of pituitary tumor whose associated headaches constitute the reason for operation

QUESTION Does the fixed chiasm ever necessitate section of one optic nerve?

DR. RAY I suppose what is meant by fixed chiasm is short optic nerves or the very prominent tuberculum sella or both In either, the space anterior to the chiasm is narrower than one would prefer In our last 100 cases I think there have been 4. In 1 or 2 patients I found at operation that this space was so narrow that I could not work conveniently or safely, therefore I had to remove the tuberculum sella This is a perfectly feasible procedure but it takes time Maybe I am impatient, but it takes me an extra half hour there is also the possibility of opening into the sphenoid sinus and of a subsequent spinal fluid leak. In one patient the visual loss occurred as the result of a fracture which passed into the optic foramen when I drove the chisel into the bone to make the first opening, so there are difficulties of that kind

In the answer to the specific question, does one optic nerve sometimes have to be divided, I would say that the answer to that is no One must make the midline exposure which I point out is a very necessary part of this particular operative technique The brain retractor must hug the falx. The surgeon's line of vision must be directly down along the falx, in which case the pituitary stalk is in full view If the exposure is compromised by a more lateral approach the right optic nerve obscures the stalk and must be retracted with a risk of damaging it. Deliberate division of the right optic nerve does not seem justifiable unless, of course, the patient is blind in the right eye

QUESTION Are you approaching your pituitary tumors from the mid line rather than from the side?

DR. RAY What I described is the method used in removing the pituitary in hypophysectomy This is still a very nice way to approach the pituitary tumor or meningioma or any other lesion in that region I must confess, though that if the frontal sinuses are very large or if the patient might object strongly if the olfactory sense should be lost I would be inclined to move a little laterally, where the frontal sinus could be avoided in the craniotomy and where one could better expect to preserve the olfactory nerve

QUESTION Are you concerned about opening into the frontal sinuses?

DR. RAY No but it is a potential risk and also, it takes a little time to deal with an open sinus when opening and closing the wound.

We also have in print at the moment, though not published, the account of 2 achromegalic patients who developed all the signs and symptoms of brain tumor and, at operation, looked as though they had glioblastomas. In each case, these changes were the results of repeated doses of x ray treatment over a period of years One can easily point out that the mistake was in giving all the x ray, but in each case the series was given by someone who thought he knew what was appropriate In each case, I think the dosage totalled somewhere around 10,000 r over a period of years. Dr Browder operated on one of these patients and I operated on the other

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CHAPTER VII

Hypophysectomy for Cancer of the Breast

BRONSON S RAY, M D

The trial use of hypophysectomy in the treatment of malignancy has been used in patients with carcinoma of the breast. I assume that you are aware that carcinoma of the breast is the commonest neoplasm in mankind. In experimental animals mammary carcinoma can be hormonally induced. In humans for many years there has been direct and indirect evidence of the hormonal influence on the growth of breast carcinoma. It seems a natural sequence then that the effects of ablation of the pituitary should be investigated after we have learned what may be accomplished by ablating the ovaries and then the adrenals, and when we have ACTH and cortisone for substitution therapy after removal of the pituitary

This report deals with the results thus far in the progress of testing the benefits of hypophysectomy in the management of advanced carcinoma of the breast in women. This work has been done in collaboration with Dr O Pearson who will speak to you shortly, and, of course, with the assistance of many people on our clinical and laboratory staffs in the New York Hospital and the Memorial Center

In the 2½ year period between March, 1954 and September 1 1956 110 hypophysectomies were performed on 109 women, and the present evaluation is based on the follow up (of from 1 to 30 months) on these 110 hypophysectomies Hypophysectomy has also been employed in a variety of other neoplasms and to date our total experience with the operation has been with about 175 patients The results in treatment of malignancies other than breast carcinoma and possibly prostatic carcinoma have been very disappointing. In fact we have seen no beneficial effects on other tumors

INDICATIONS FOR HYPOPHYSECTOMY

The indications that we have come to employ in recommending and performing hypophysectomies on women with carcinoma of the breast are that there should be palpable or visible lesions evidencing metastasis or there should be x ray evidence of metastasis to lungs or bone or pleural effusion containing identifiable malignant cells Some patients with skeletal metastases also have alteration in calcium balance (hypercalcemia and hypercalciuria) In fact in choosing patients on whom to perform the

operation, we did not choose any who have not shown evidence of metastatic disease in progressive activity. With patients who have recently been treated by some other means, with estrogens or androgens or x-ray or cortisone, we have waited until the effect of this treatment had worn off, if indeed there had been an effect and when we were sure that we were dealing with an active process. Otherwise, we should have had nothing with which we could make comparison after the hypophysectomy.

We have found no evidence of correlation in our results with the type of tumor of the breast, with the age of the patient or the duration of the disease, that is the interval between the discovery of the disease or mastectomy and the time of hypophysectomy. Patients with intracranial metastases evidenced by increased intracranial pressure, palsies, aphasia or confused mental states have been excluded. Patients with serious impairment of their vital capacity as the result of metastases to the lung have been found to be unsuitable. This does not mean, however, that patients are excluded who have respiratory difficulty from pleural effusion, if this symptom is overcome by draining the fluid. Often pleural metastases appear to benefit from hypophysectomy and pleural fluid does not reaccumulate after operation. Also, it has seemed that patients with extensive liver metastases, those which would produce a very large liver, jaundice or some measurable deficiency in liver function, do poorly after hypophysectomy. But often, as it must be obvious to you, the decision has to be arbitrary and depends pretty much on that intangible factor, clinical judgment. On the whole, the patients of this series have had advanced metastatic disease and many of them have been seriously ill.

A SATISFACTORY SURGICAL TECHNIQUE

After an initial period of trial and error with the surgical techniques, we arrived at a satisfactory method in March 1954. The patients who are evaluated in this present report were operated on after that date and by the same method (except for a few minor variations in technique). I performed all the operations. If there is time later a film of the operative procedure can be shown, but I should like to go on here to discuss the results of operation which are more important at the moment.

Dr Pearson will discuss with you in more detail the various endocrine aspects of the problem. In the 18 hours before operation patients were given 300 mg. of cortisone, in divided doses, intramuscularly, on the morning of operation 100 mg. of cortisone were given by mouth and following the operation cortisone was continued intramuscularly for 24 hours in 50-mg. doses given every 4 hours. Thereafter for the following week the dosage of cortisone was gradually diminished to the maintenance dose of about 25 mg. twice in 24 hours. The matter of controlling diabetes insipidus

thyroid deficiency and other occasional postoperative endocrine problems will be discussed by Dr Pearson

Perhaps we cannot talk with complete certainty about how many patients have had incomplete hypophysectomy but my estimate is that in this group of 110 operations there are 6 known incomplete hypophysectomies In the patients who have died there is an autopsy rate of about 50 per cent Serial sectioning on the region of the sella turcica has not been made in all the patients that have come to autopsy It is an expensive and time consuming procedure and it has not been practical to perform serial sections on every autopsy specimen In those patients who—in clinical tests—were believed to have residual gland, there was residual glandular tissue, evident on gross inspection In those believed to have had total hypophysectomy on the basis of endocrine studies, residual glandular tissue was not present on serial sections, with one possible exception

The first slide (Table 5) shows you the postoperative morbidity and mortality rates Among the 109 patients there were 8 deaths within the first 30 days after operation Three of these are estimated to be the direct result of the surgical procedure One patient believed to have a postoperative remission of her disease had gone home but died of a pulmonary embolism on the 26th day One patient died before the skin incision could be completed, probably as a result of unrecognized pericardial metastases There were 3 patients who died in this 30-day period of the progression of their disease having been unbenefited by the hypophysectomy Therefore, the over all mortality (that is, death within the first 30 days after operation), is about 7 per cent The mortality directly attributable to operation is nearer to 3 per cent, it might be as low as 2 per cent and certainly is not more than 5 per cent.

The morbidity is listed as follows 2 patients sustained important visual loss One of these patients lost vision completely in one eye but in the

TABLE 5
Risks of Hypophysectomy in 110 Operations

Mortality (30 days postoperative)	
Direct surgical	3
Pulmonary embolus (26th day)	1
Anesthesia	1
Progression of disease	3
Morbidity (13 patients)	
Serious visual loss	2
Field defects	5
Neurological complications	3
Intracranial clot	3

other eye she has enough vision left for useful purposes The other patient had considerable impairment in both fields of vision but returned to her job as hairdresser Six others had field defects which were identified only on careful visual field studies or were recognized by patients as very minor quadrantic defects Three are listed as having neurological complications, mostly hemiparesis, but one patient had aphasia which we have found difficult to understand since she was right handed Recovery was enough in these 3 so that residuals were not important Three had postoperative intracranial clots that required re-operation, but in the last 30 or 40 cases this complication has not recurred, for reasons which I shall mention later To this morbidity list should perhaps be added 2 things—one is that about 5 to 10 per cent of patients have had convulsive attacks, sometime in the first week after the operation. To minimize the likelihood of this occurring, *we now administer Dilantin several days before operation* and continue it for 10 days to 3 weeks afterward The other thing that should be mentioned is that at least half of the patients lose smell functions for it does not seem possible always to avoid damage to both olfactory nerves. Fifty per cent is an estimate, because it has seemed better not to draw attention to the possibility of the loss of smell. Some of those that have lost smell function are well aware of it, others are not or ignore it or accept it as something unimportant

The next slide (Table 6) lists the criteria for evaluating remission of the metastatic disease by hypophysectomy We have kept definitely and rigidly to objective signs of remission and disregard subjective improvement alone as reliable evidence of remission. Patients are regarded as having developed remission when either *arrest of the disease* or *regression of the disease* has occurred An *arrest* has occurred if there is no progress of the previous lesion or if there is disappearance of hypercalcemia and hypercalciuria or improvement in myelophthisic anemia accompanying extensive skeletal metastases. Evidence of *regression* includes 1) Recalcification of bony lesions that is by x ray 2) Diminution in size of any visible or palpable

TABLE 6
Criteria for Evaluating Remission

Arrest
No progress of previous lesions
Disappearance of hypercalcemia and hypercalciuria
Improvement in myelophthisic anemia
Regression
Recalcification of bone lesions
Diminution in size of any lesion
No new lesions



Fig VII 1a

lesion and, at the same time no new lesion Remission is counted as having ended when any old lesions become progressive or new ones appear It is only fair to say that relief of pain in patients with bony metastases has often been dramatic I almost hesitate to report that when some patients wake up they are completely relieved of the severe pain they suffered before It seems a little too dramatic but such is the case Occasionally there has been relief of pain when it was not possible objectively to establish regression of the skeletal lesion.

The following slides show a few examples of objective remission The first (Fig VII-1a) is a preoperative picture of an ulcerating lesion of the breast in a 42 year old woman In 1952 she had been castrated for what was considered to be an inoperable tumor mastectomy was not performed



Fig VII 1b

Eighteen months ago hypophysectomy was performed and the next photograph (Fig. VII–1b), made 11 months after operation, shows the resolution of the tumor The remission of her disease continues now 18 months following hypophysectomy

The next case (Fig VII–2a) is that of a 72 year-old woman who had an extensive tumor extending well up in the supraclavicular region, axilla, arm, across the other side and down toward the abdomen circling a good part of the chest. She had no other metastases and she had no other treatment The postoperative picture (Fig VII–2b) taken one year later shows the complete subsidance of her extensive lesions Her remission ended shortly after this picture was taken about a year after hypophysectomy but she is still living more than 2 years after hypophysectomy The local recurrence has been slow and has responded rather well to x-ray treatment and she has not developed any other metastases

The next slide is of roentgenograms before and after operation (Fig VII–3) of a 34-year old premenopausal woman who had a radical mastectomy and local x ray treatment 2 years before hypophysectomy She had developed pulmonary symptoms 2 months before she came to the hospital with the

Fig VII-2a



Fig VII-2b

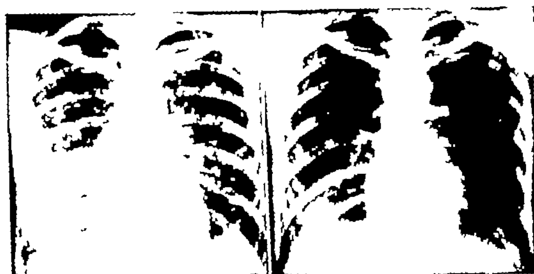


FIG VII-3

roentgenogram. The second roentgenogram was made just 3 weeks after operation and shows the rapid disappearance of the pulmonary lesions It is now 18 months since operation and her disease is still in full remission. She is a good looking school teacher and is teaching school and leading just as active a life as ever I emphasize the fact that she is good-looking to bring out the point that patients after hypophysectomy do not have a change in features. They do not look like patients with hypopituitarism and they are spared the changes in appearance that accompany androgen therapy or large doses of cortisone

The next slide shows pre- and postoperative films (Fig. VII–4) of a 42 year-old woman who had a radical mastectomy 2½ years before. One year before hypophysectomy she had castration for metastasis to the lungs, and had a favorable result from that for about 6 months The first film



FIG. VII-4

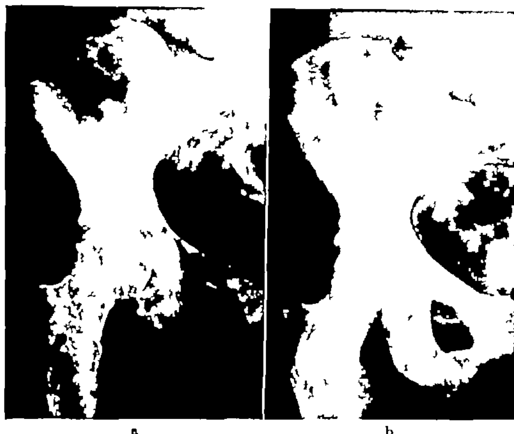


FIG. VII-5

shows the extensive recurrent pulmonary metastases and also pericardial effusion due to pericardial metastases The postoperative film 4 months later shows the remarkable subsidance of the lesions Full remission ended about 10 months after operation

The next slide shows pre- and posthypophysectomy films of skeletal metastases (Fig VII–5) in a 44-year old woman who had a radical mas tectomy 4 years before Skeletal metastases were known to exist during the 18 months before hypophysectomy The striking improvement in the appearance of the skeletal metastases after an interval of about 6 months is seen in the postoperative film Remission ended some months after that, but the temporary effect was quite dramatic

RESULTS OF HYPOPHYSECTOMY IN MAMMARY CARCINOMA

We have tended to compare our results with those of Luft and Olivecrona Luft recently brought their statistics up to date in a paper presented before the American Cancer Society in New York. He reported remission of disease after hypophysectomy in 54 per cent of 52 patients with mam mary carcinoma. Our results have been quite comparable and our opinions are not at significant variance with one possible exception They make a

TABLE 7
Results of Premenopausal Hypophysectomy (8 cases)

Arrest of disease (2 and 5 months)	2
Regression of disease (7 4+ 17+ months)	3
No benefit	3

point that hypophysectomy has little or no benefit in older women and that has not been our experience at all You have seen the dramatic improvement in a 72 year-old woman, and in others over 60 years of age there have been comparable benefits

All the cases of Luft and Olivecrona were of primary hypophysectomy, that is their patients had not had previous castration or adrenalectomy A third or more of our patients have had hypophysectomy after they have had castration, or castration and adrenalectomy and it is possible therefore to point out that additional benefits can be attained from hypophysectomy after castration and adrenalectomy

The following slides will show the results in several groups having a different endocrine status Eight patients were in the premenopausal period and still menstruating (Table 7) Two of the 8 had an arrest of from 2 to 5 months after hypophysectomy and 3 others had regression of their disease Of the 3 patients whose disease regressed after hypophysectomy, 2 are still in a state of regression 4 and 17 months later, while one has had reactivation of the disease 7 months after hypophysectomy

The next slide (Table 8) classifies the results in 25 patients who had therapeutic castration either surgically or by x ray before hypophysectomy Of these 25 patients 14 had remissions 9 failed to improve, and 2 cannot yet be evaluated. An observation of additional interest and importance is that the 7 patients who had a temporary remission of their disease from castration have a new remission following hypophysectomy In 1 of 5 patients who had failed to benefit from castration a remission occurred from hypophysectomy It is very likely, therefore that any patient who benefits from ablation of the ovaries can be expected to benefit also

TABLE 8
Results of Hypophysectomy in 25 cases with Previous Therapeutic Castration

No benefit	9
Remission of disease	14
Not evaluated	2

Response to castration	7 Response to hypophysectomy
5 No response to castration	1 Response to hypophysectomy
13 Unevaluated castration	6 response to hypophysectomy

TABLE 9
Results of Hypophysectomy in 12 Cases with Previous Therapeutic Castration and Adrenalectomy

No benefit	8
Arrest of disease (for 2 to 3 months)	3
Regression of disease (for 7 months)	1

from hypophysectomy and that occasionally patients who do not benefit *from castration may benefit from hypophysectomy* *There were 13 patients* in whom the results after castration could not be adequately evaluated, half of those patients obtained a remission from hypophysectomy

The next chart (Table 9) is *of a group of 12 patients who had had* oophorectomy and adrenalectomy Three patients had arrest of the disease for short periods, (2 to 3 months) and 1 patient had had a regression of the disease lasting for 7 months. This is definite evidence that something more is accomplished by hypophysectomy than is accomplished by a combination of oopherectomy and adrenalectomy It might be reasoned that those who benefited did so as a result of suppression of function of accessory adrenal tissue but it does not seem likely that this would be true for as many as 4 of 12 patients.

The next slide (Table 10) pertains to patients in postmenopausal phases Of the 56 patients there were 28 who had remissions, 24 who failed to benefit and 4 who have not yet been evaluated Thirty eight had had spontaneous menopause and 18 induced menopause prior to developing carcinoma of the breast. There does not seem to be any significant difference in the results of hypophysectomy in the two groups

The final slide, (Table 11) summarizes the results of 110 hypophysectomies in 109 patients over a 2½ year period Fifty-one patients had remission of their disease (10 were *arrests* and 41 were *regressions*) There were 44 failures and 8 deaths. The results in 6 patients have not yet been determined.

The average duration of the objective remission so far is 7 6 months—the shortest period of remission being 2 months and the longest to date being 27 months (in a patient who shows no signs of recurrence of the disease) It is of course encouraging to add that 23 of the 51 patients

TABLE 10
Results of Postmenopausal Hypophysectomy in 56 Cases

No benefit	24
Remission of disease	28
Not evaluated	4

TABLE 11

Results of Hypophysectomy in 100 Cases of Breast Carcinoma

No benefit	44
Deaths	8
Arrest of disease	10 } 51
Regression of disease	41 } 51
Not evaluated	6
Average duration remission (to date)*	7 6 months

* Extremes 2 to 27+ months. 23 of 51 still in remission

are still in remission and the average duration of remission will increase as time passes Luft reports an average period of remission of 17 months

It is gratifying to show objective improvements for a while in patients, but the question inevitably asked is 'are we prolonging life and doing it so for the comfort of the patient? In attempting to draw some conclusion regarding the survival time we found that the average period of survival following hypophysectomy in patients who had not benefited by the peration (not counting the postoperative deaths in the first 30 days) has een 5 months and but a few of the patients in that group are still living. gainst that we can compare the survival thus far in the patients who ve been benefited by operation and already it is better than twice as ng. That is, the survival period is 10 months or better, with half the pa- nts still in remission and still living. Of course the termination of remis- n is not synonymous with the termination of life There is some sugges- tion too that in some patients the disease is mild and slow in its recurrence and that the beneficial influence of hypophysectomy continues

OTHER TECHNIQUES FOR ABOLISHING THE PITUITARY AND ITS FUNCTION

I am sure that you are well aware that others have tried and are trying different techniques for abolishing the pituitary or its function. These other techniques include section of the pituitary stalk without removal of the gland and intracranial approaches for the excision of the gland different from the one I have shown Transantral excisions have been tried and are being tried again. The insertion of radioactive material by way of intra cranial exposure or transantrally is being investigated in some places. Then there is irradiation of the pituitary either by betatron or, as more recently reported by Dr John Lawrence, by use of a proton beam produced by a linear accelerator

These methods are designed to avoid the hazards of intracranial hypophysectomy but few of them consistently attain total excision of the gland or abolition of pituitary hormones Our efforts have been directed

toward finding out first of all what can be accomplished by total ablation by intracranial excision of the pituitary Against this experience we can evaluate the efficacy of other methods

12 MINUTE TECHNICOLOR 16-MM. FILM OF THE

SURGICAL TECHNIQUE OF HYPOPHYSECTOMY

Movie Comment The incision formerly employed was right frontal with one limb passing vertically through the mid-forehead, but I have given this up in favor of a coronal incision just behind the hairline. A concealed scar is much appreciated by these women who have already had to suffer a great deal Anesthesia is induced by Pentothal sodium and maintained by endotracheal ether Hypotension induced with Arfonad usually is started before the skin incision is made and is continued until the closing skin sutures are in place. The patient lies in the supine position sometimes with the head dropped back and often with the table tilted with the foot down in order to facilitate the effect of hypotension The systolic blood pressure is maintained somewhere around 70 mm of mercury

A free bone plate is removed from the right frontal area A transverse incision through the temporal fascia near its attachment is done in such a way that the fascia and muscle can then be sutured back in place at the time of closure That does away with the unsightly depression in the temporal region. One of 4 preliminary openings in the skull is low in the midline of the forehead made with a trephine The removal of a bone button here not only makes it possible to replace it in closing and thus avoid dimpling but also it often serves to hold in place sealing material Gelfoam or a piece of the periosteum or some other material against an open frontal sinus if the frontal sinus has been opened inadvertently or deliberately I have learned not to compromise the exposure by altering the position of this bur hole and the sawcut through the brow even if the frontal sinuses are large. If the frontal sinus is large it is often possible to push back the mucosa and preserve it so that there is no opening into the cavity of the sinus. If the sinus is opened it is temporarily packed off during the operation and at closure it can be sealed off by any one of a variety of methods If the opening in the sinus is large I turn a flap of the periosteum down over the margin and anchor it to the dura. If the opening is small usually Gelfoam held in position by the replacement of the bone plate and the bone button is sufficient Rarely have we encountered temporary cerebrospinal fluid rhinorrhea and thus far have had no important infections.

After the bone plate is removed and the dural opening started spinal fluid is removed through a needle which has been placed at the beginning of the operation. This is an intradural approach and I am sorry I did not

see Dr Love's picture yesterday about which I have heard such fine comments. I understand he made a point of staying outside the dura as far as possible, but I have had no reason to feel that we were in any difficulty in using this intradural type of approach It is most important to stay up close to the falx. The surgeon's line of vision must be directly down the line of the falx so that it is possible to see between the optic nerves The olfactory nerve on the right is divided The reason why patients sometimes lose smell function is that the nerve on the left will tear when the brain is retracted

After the withdrawal of all the spinal fluid one can expect to get a view of the hypophyseal stalk and adjacent structures The only exceptions are when the tuberculum sella is prominent or the nerves are relatively short The stalk in this case is coagulated to diminish bleeding when it is cut and also to destroy any anterior lobe cells that may extend into it I am satisfied now that coagulation is not a wise procedure since the incidence of permanent diabetes insipidus is much less if the stalk is sharply divided at the level of the diaphragm sellae without previous coagulation or clipping. After the stalk has been divided the maneuver is to plunge the blunt end of a hook through the opening in the diaphragm and tear the diaphragm in a cruciate fashion to the margins of the circular sinus. Ring curettes of several sizes and shapes some sharp and some semi-sharp, are used to clean out the cavity of the sella turcica systematically The gland is usually removed in several large pieces and then small remaining fragments are obliterated by systematic currettement abrasive swabbing, suction and finally exposure to Zenker's solution.

Of principal concern, I find is deliberate interruption or accidental tearing of large veins that run into the saggital sinus This is likely to lead to venous congestion subpial or even subcortical hemorrhage When it comes time to close the wound if the tip of the frontal lobe looks as though it has been jeopardized by the interruption of the veins the tip of the lobe should be resected Complications leading to postoperative deaths in 3 patients ocurred is a result of failure to follow this procedure

Application of Zenker's solution to the walls of the sella is accomplished by placing in the cavity a small rubber sponge into the center of which has been implanted the end of a polythene tube A small pledget of cotton is packed under the chiasm to plug the subarachnoid space to protect against any possible spillage of Zenker's into the basal cisterns Actually there has been no difficulty or complication from this maneuver but one can never get *careless* It is less important how much Zenker's solution is used for irrigation than the time during which the cavity of the sella is exposed to the solution usually ten minutes exposure leaves a gray coagulated lining of the sella. Before taking the sponge out it is necessary

to run saline through it to remove the Zenker's solution and thus protect the optic nerves as the sponge is removed.

On closing the wound the spinal fluid need not be replaced The dura has always been approximated tightly, particulary if there has been an opening in the frontal sinus. There has been no trouble with edema of the brain and there is no need for a decompression

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Luft R. and H. Olivecrona Hypophysectomy in Man Experiences in Metastatic Cancer of the Breast. Cancer March and April 8, 261 No 2, 1955

Luft R. and H Olivecrona Hypophysectomy in the Treatment of Malignant Tumors. Cancer (In Press) Presented at the Scientific Session of the American Cancer Society New York, October 1956)

Questions and Answers

Question What are the results of transection of the pituitary stalk, as compared to hypophysectomy in the treatment of metastatic carcinoma?

Dr. Ray It has been my impression that it is virtually impossible to draw any conclusions from the results of the procedure, but perhaps I am not up to-date on the matter

I know that the operation was performed on the basis of work done by Harris and others in England It may be that this will turn out to be a useful procedure, but on the information we have in hand at the present, I don't see how that can come about Certainly, in our operations for removing the pituitary we cut the stalk—there is no question about that We know that if there is any significant part of the pituitary gland left there is still identifiable anterior lobe function If that is not done away there is still identifiable anterior lobe function. We shall have to change our whole attitude, if it turns out that we can get clinical benefit by simply dividing the stalk and still have evidence of pituitary activity I would not be inclined to expect much from stalk section but I would keep an open mind

CHAPTER VIII

Physiological Effects of Hypophysectomy

OLOF H PEARSON, M.D

When Dr Ray and I first discussed hypophysectomy we were of course, concerned about what would happen to the patient after removal of the pituitary This was at a time when cortisone was available for replacement therapy We had had experience with the use of cortisone in patients with Addison's disease and with removal of the adrenal glands and we were quite confident that, as far as adrenal function was concerned these patients could be quite adequately maintained. Also patients with panhypopituitarism could be maintained in a good state of health with adequate adrenal and thyroid replacement

ADRENAL FUNCTION

I would like to discuss first the effects of removal of the pituitary gland on adrenal function (1) The adrenal glands are most important as far as life maintenance is concerned Following hypophysectomy there is a profound cessation of function of the adrenal glands comparable to that of surgical removal at least as far as life maintenance is concerned. The hormones of the adrenal glands, as we know them now, consist primarily of hydrocortisone which is the life maintaining hormone In addition to hydrocortisone there is the salt hormone known as aldosterone As I will demonstrate following hypophysectomy this function of the adrenal gland is apparently not impaired so that maintenance of salt balance is not a problem after hypophysectomy as it is after adrenalectomy In addition to hydrocortisone and aldosterone the adrenal gland produces androgenic and estrogenic steroids One of the purposes of hypophysectomy is to suppress the production of these steroids since they may be important in the growth of breast cancer

Figure VIII–1 illustrates some of the things that happen to an adrenalectomized patient on withdrawal of cortisone The patient was being maintained on 50 mg. of cortisone a day given in divided doses of 25 mg every 12 hours plus an adequate salt intake When cortisone was withdrawn, the patient noted malaise anorexia and lassitude within 24 hours. There-

* These studies were supported in part by grants from the National Cancer Institute of the National Institutes of Health United States Public Health Service the United States Atomic Energy Commission the American Cancer Society Inc and the Damon Runyon Memorial Fund

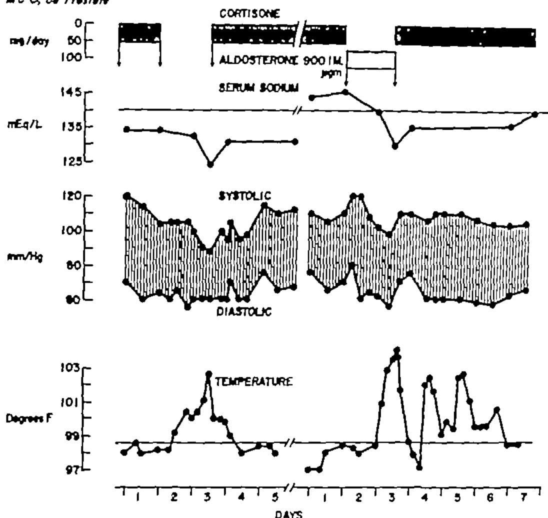


FIG VIII-1 Effects of withdrawal of cortisone in an adrenalectomized patient on body temperature blood pressure and serum sodium

after muscular aching postural hypotension nausea, and profound weakness ensued. At 36 hours the patient had an ashen gray appearance, was hyperpyrexic and hypotensive and appeared critically ill Replacement with cortisone brought the patient back to normal within 12 to 24 hours Similar changes occur in the hypophysectomized patient when cortisone is withdrawn In the adrenalectomized patient, the serum sodium frequently falls although this is not invariable After hypophysectomy this is less likely to occur because, we think there has been damage to the pars nervosa system producing a mild diabetes insipidus.

Figure VIII-2 demonstrates that the hypophysectomized patient can maintain a normal salt balance on a low salt intake This patient was maintained on desiccated thyroid 2 grains a day, and 50 mg. of cortisone daily The sodium intake was decreased from 144 to 10 mEq per day

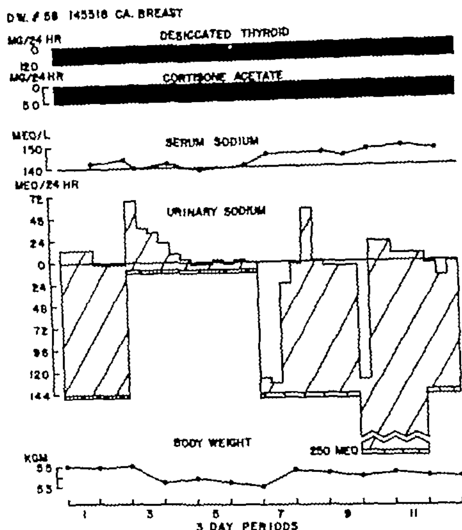


FIG VIII-2 Effects of alterations in sodium intake on the sodium balance of an hypophysectomized patient. The sodium intake is plotted downward from the zero line and the fecal and urinary sodium output is plotted upward from the intake line

Sodium balance was attained by the sixth day The serum sodium remained normal and the patient felt well This *response is similar* to that of a normal individual. It has been demonstrated that the hypophysectomized patient does excrete aldosterone in the urine and that the amount increases when the sodium intake is reduced

Figure VIII-3 illustrates the effects of salt withdrawal in a patient with Addison's disease When the sodium intake was lowered to 10 mEq per day sodium balance was not achieved after a period of 15 days At this time the patient developed weakness and anorexia which disappeared promptly when the salt intake was restored.

THYROID FUNCTION

Hypophysectomy induces a marked suppression of thyroid function resulting in clinical manifestations of hypothyroidism within 4 to 8 weeks

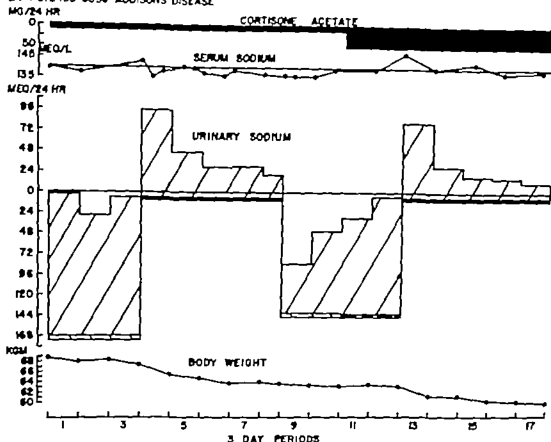


FIG. VIII-3. Effects of variations in sodium intake on the sodium balance of an Addisonian patient.

(2) We have avoided giving thyroid replacement therapy for several weeks after operation because we felt that evaluation of thyroid function might provide information concerning the completeness of hypophysectomy Figure VIII-4 presents the changes in serum protein bound iodine in a group of patients before and after hypophysectomy It will be noted that the values fall to myxedema levels within 2 weeks after operation Figure VIII-5 demonstrates the uptake of radioactive iodine by the thyroid gland in the same group of patients Hypophysectomy markedly impaired the ability of the thyroid gland to accumulate radioactive iodine If hypophysectomy has been grossly incomplete, these parameters of thyroid function may show an initial decline but usually return to normal within 3 to 4 weeks after operation. Thus, measurements of thyroid function provide a valuable check on the completeness of hypophysectomy but do not necessarily guarantee that a 100 per cent removal of the pituitary gland has been obtained.

The serum cholesterol rises very slowly after hypophysectomy and the increase is relatively minor averaging 60 mg./100 cc.

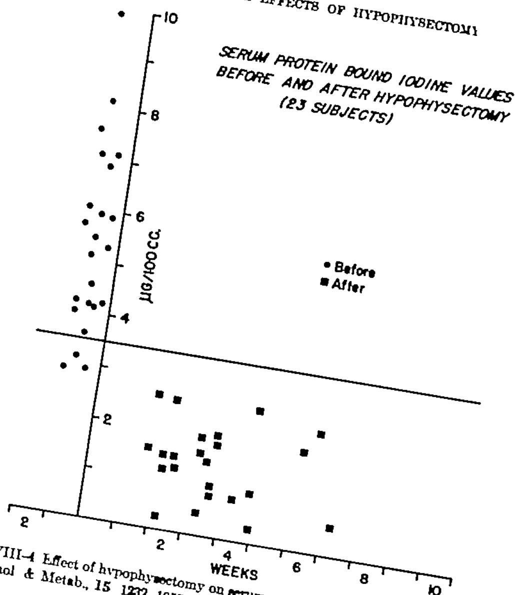


Fig VIII-4 Effect of hypophysectomy on serum protein-bound iodine From J Clin. Endocrinol & Metab., 15 1232 1955

The length of time for the development of clinical hypothyroidism is quite variable occasionally taking 4 to 6 months but usually being evident within 1 to 2 months Earliest signs of hypothyroidism have been dryness of the skin and obesity Subsequent appearance of the classical clinical manifestations of myxedema such as cold intolerance constipation lassitude thickening of the skin and delayed relaxation phase of deep tendon reflexes have been observed when thyroid is withheld Restoration to the euthyroid state has been easily accomplished with 120 to 180 mg. of desiccated thyroid daily

GONADAL FUNCTION

In menstruating women function of the ovary appears to cease after hypophysectomy When the operation was done early in the menstrual

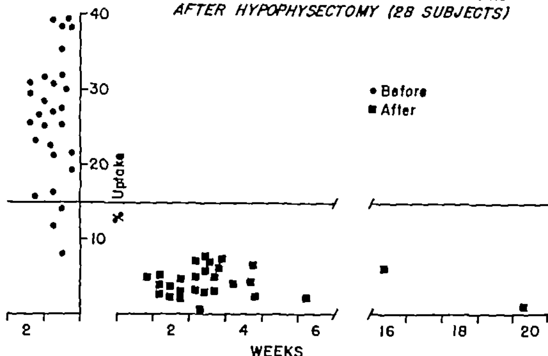


Fig. VIII-5 Effect of hypophysectomy in the 48-hour I^{131} uptake by the thyroid gland. From J Clin. Endocrinol. & Metab., 15, 1231 1955

cycle, no further menstrual periods occurred. If the operation took place during the progestational phase, there was one subsequent mensis The vaginal smears show a postmenopausal picture one week after hypophysec tomy and a completely atrophic smear is obtained in 2 to 4 weeks.

Pituitary gonadotrophin excretion in the urine has been measured as another index of the completeness of hypophysectomy In the majority of cases a complete hypophysectomy was accompanied by disappearance of gonadotrophins 2 to 3 weeks after operation. A few patients who were subsequently proved to have had complete removal of the pituitary gland have exhibited persistence of urinary gonadotrophins for periods of 2 to 3 months before the titer dropped to an immeasurable level.

None of the premenopausal patients suffered definite postmenopausal symptoms after hypophysectomy Two patients had transient peculiar sensations simulating vasomotor phenomena but severe hot flushes' as may occur following ovariectomy have not been encountered.

There is a marked decrease in growth of axillary and pubic hair which may become quite sparse Scalp hair appears to grow normally and retain its previous texture Female patients have noted a definite decrease in libido following hypophysectomy

Our observations of the effects of hypophysectomy in males with intact

testes have been limited In two patients, the testes became small and soft within 4 to 6 weeks after operation Atrophy of the sex organs occurred and the patients were impotent A testicular biopsy obtained 6 weeks post-hypophysectomy showed considerable atrophy of the tubules.

OTHER PITUITARY FACTORS

The hypophysectomized patient who is maintained with cortisone and thyroid retains a normal appearance and, in particular, the color and texture of the skin does not reveal any obvious change Pallor of the type seen in the untreated hypopituitary patient has not been encountered. Our patients tan normally when exposed to sunlight and do not appear to have any undue sensitivity to such exposure. Thus, the presumed absence of melanophore-stimulating hormone does not produce any gross changes in the skin.

Observations on carbohydrate metabolism were made as a possible reflection of the lack of growth hormone Alterations in carbohydrate metabolism following hypophysectomy have been minimal No instance of symptomatic hypoglycemia has been encountered With cortisone maintenance the fasting blood sugar is either unchanged or shows a minimal drop (10 to 15 mg./100 cc) The oral glucose tolerance test is either normal or may show a slight exaggeration of the late hypoglycemic phase When the hypophysectomized patient is maintained with cortisone insulin tolerance appears to be somewhat reduced although hypoglycemia responsiveness is normal. We tested our patients following hypophysectomy with one-third or one-half the usual does of insulin and obtained normal insulin tolerance curves, which were comparable to insulin tolerance curves obtained before hypophysectomy using the the standard insulin dosage (0 1 units per kg.) Two cancer patients with diabetes mellitus who required moderate amounts of insulin did not require insulin after hypophysectomy These observatins suggest that hypophysectomy induces minor changes in carbohydrate metabolism possibly related to the presumed absence of growth hormone

The hypophysectomized patient is able to gain weight without the addition of gonadal steroids. Positive nitrogen balance may occur in the absence of growth hormone or androgens Pathological obesity has not been encountered. Repair of bone can occur after hypophysectomy as evidenced by the appearance of callus in osteolytic lesions and pathological fractures In patients whose cancer remained quiescent no evidence of anemia developed after periods up to 2 years after hypophysectomy In 2 cases myelophthisic anemia due to cancer regressed after hypophysectomy, so that bone marrow can restore itself to normal in the absence of hormones other than cortisone and thyroid Androgens exert their typical anabolic

effects in these patients Estrogens will induce vaginal cornification and endometrial proliferation, as evidenced by withdrawal bleeding.

DIABETES INSIPIDUS

When the hypophyseal stalk is cut and the pituitary gland removed, a major portion of the pars nervosa has been destroyed. If the stalk is sectioned below the diaphragma sellae, as is done in transsphenoidal hypophysectomy (3), permanent diabetes insipidus was not encountered. When the pituitary stalk was sectioned and cauterized above the diaphragma sellae, more than 90 per cent of the patients developed varying degrees of diabetes insipidus In this discussion, diabetes insipidus is defined as that state characterized by a decreased renal concentrating ability without reference to polyuria although polyuria is usually present. It is our belief that at equal solute loads the severity of the diabetes insipidus depends on the level of stalk section and the preservation of a variable portion of the pars nervosa.

Following transfrontal hypophysectomy, polyuria may appear within a few hours to a few days (4) Within a period of about 2 weeks postoperatively the water exchange usually stabilizes at a level which persists indefinitely thereafter In some patients the daily water exchange may be only twice the preoperative level, although the solute load is unchanged There is a range from these mild cases to those patients who have daily urine outputs of 9 to 10 liters per day In the mild cases, dehydration may induce considerable concentration of the urine whereas in the severe cases there may be little or no ability to concentrate the urine. As indicated above, it is believed that the degree of severity of the diabetes insipidus is dependent upon the remainder of the pars nervosa which remains intact.

The presence or absence of the anterior lobe of the pituitary does not appear to be a determining factor in the degree of diabetes insipidus which develops Withdrawal of cortisone in the hypophysectomized patient with polyuria usually results in a decreased urinary output. It has been shown that this decrease in polyuria results from the decreased solute load presented to the kidney due to the associated anorexia and that there is essentially no increase in the concentration of the urine Variations in the doses of thyroid and cortisone replacement have produced no significant changes in renal concentrating ability in patients with diabetes insipidus

In patients who have mild polyuria moderate restriction of salt intake may be sufficient to bring the water exchange within the limits of comfort. For more severe cases of polyuria most patients prefer the use of posterior pituitary powder (Armour) by nasal insufflation 3 or 4 times daily for relief Pitressin tannate-in-oil (Parke Davis) given intramuscu

larly in doses of 5 units every 2 to 4 days will also provide effective relief of the diabetes insipidus

In conclusion, it can be stated that replacement therapy is adequate for maintenance of normal life after total hypophysectomy in man

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Questions and Answers

Question to Dr. Love Do you select cortisone over ACTH in pituitary tumor cases and would not the patient be better off with ACTH?

Dr. Love As you have already heard, cortisone is the life-sustaining substance or hormone of the adrenal gland. ACTH on the other hand, is a stimulant to the adrenal gland. We administer cortisone intramuscularly in 200-mg doses, and we do this to assure the patient of a store of this substance which will fortify him against the stress and strain of both the anesthesia and the surgical procedure that is anticipated. ACTH of course will stimulate the adrenal glands to produce the natural product cortisone I believe it is generally accepted that cortisone protects the patient better in such a circumstance than would ACTH I am not, however, an endocrinologist, and I think the answer to the second part of the question ought not to come from me

Question to Dr. Ray Please comment on the last question and would you reiterate the pre- and post-operative endocrine assistants that you use.

Dr. Ray I agree with Dr Love that cortisone is the more practical means of handling the shortcomings of the adrenals because it doesn t do any good to whip a tired horse There is little way of knowing where you stand if you rely on ACTH during the stress period of an operation or immediately thereafter You are in a much better position if you use cortisone Furthermore, if the patient is to take one or the other of these drugs for any length of time cortisone by mouth is much more readily available to the patient than ACTH injection. With regard to aldosterone as Dr Pearson reported to you the aldosterone production is not dependent on the pituitary gland It might then easily be assumed that we don t have

any difficulty with salt balance after hypophysectomy and are not confronted with salt losing syndrome after operation in patients with pituitary tumors. That does not always seem to be the case and many surgeons are now aware of the difficulty in controlling the low salt syndrome that occasionally develops in the post-operative management of pituitary operations, this problem needs a great deal of investigation. The chances are that in addition to the aldosterone hormone, there is a central mechanism that also controls salt balance, and if your patient does poorly in the post operative period in spite of your careful administration of cortisone, you had better make very sure about the electrolyte situation. If the sodium chloride is low, just accept that for what it is and deal with it as needed. You may not be able to explain it as yet, but the fact remains that I think that in the past some of the deaths in the post-operative period, had been the result of insufficient salt In the patients with carcinoma of the breast, of course there may be unsuspected metastasis to the adrenals and in that case the aldosterone production could be affected.

Question to Dr. Ray Will you summarize the post-operative tests and your criteria for assuming that the hypophysectomy has been complete, also, what treatment you would use afterwards?

Dr. Ray I am not an endocrinologist but I have learned some of their lingo and I have given careful attention to the tests that have been employed in our series of patients. The routine tests have been the evaluation of the thyroid function by the iodine studies (principally the I 131 uptake with the protein bound iodine determinations) We believe that the value is reduced to a low level permanently if the pituitary has been completely removed. If there are exceptions to this they must be quite rare and as yet need explanation. That is one way we expect to determine how complete the hypophysectomy is

Another test is the study of the F.S.H production which has to do with the gonadotropic hormone and which should disappear completely after hypophysectomy However sometimes in an incomplete removal of the pituitary both in animals and in man the iodine determinations and F.S.H determinations fall to zero yet there may still be some functioning gland. In experimental progressive destruction of the pituitary the gonadotropic hormone and the follicle stimulating hormone are abolished first, whereas the ACTH (the adrenotrophic hormone) is the last to disappear A little residual gland will be enough to continue production of the adrenotrophic hormone

Finally if you want to test your patient, take him off cortisone and watch him carefully If he has any residual functioning gland he will be able to go along for many days if not continually without cortisone if he has total removal of the gland he will very soon let you know Within

not more than a week's time, he will probably develop Addisonian crisis and will not be able to withstand the permanent withdrawal of cortisone. These are the tests on which we have relied in determining completeness of hypophysectomy However, the accuracy may be open to question and some have questioned it Dr Pearson, whose ability and opinion I have come to regard highly, is very much satisfied with it Our treatment, as I outlined to you in chapter VII, is to fortify the patient with 300 mg. of cortisone in the 18 hours before surgery, add about 200 mg. on the day of operation, and gradually (in a week's time) diminish the amount to a maintenance dose of 25 mg. twice a day—that is, 50 mg. in a 24-hour period, which he must take thereafter If he misses a dose, or two nothing bad is going to happen It isn't quite like insulin. But if he misses several days dosage, he will certainly get into trouble

DR. LOVE There is one point I forgot to mention and since no one else has mentioned it, I shall elaborate on it We have indicated that if the patient is doing satisfactorily, we cease to administer cortisone a few days after removal of a pituitary tumor But if some untoward sign or symptom arises, such as manifestations of a clot or the necessity for opening the wound or an emergency situation such as acute appendicitis or renal colic we would of course wish to fortify the patient This we can do now, as you probably know, by means of hydrocortisone, which can be administered intravenously Moreover if a patient is encountered who exhibits the signs of hemorrhage into an adenoma and an emergency operation is required at once it is not necessary to delay surgical intervention until the patient has been prepared with cortisone administered intramuscularly The operation can be conducted immediately and the hormone can be administered while the operation is in progress with adequate protection to the patient

QUESTION TO DR. RAY Is it not true that some anterior lobe must be present for the development of diabetes insipidus?

DR. RAY This of course was the attitude for many years based on experimental work in animals but we believe that it is erroneous We believe that diabetes insipidus is entirely dependent on degeneration of the supraoptic and paraventricular nuclei and its occurrence is no criterion as to whether there is or is not any anterior lobe present

QUESTION TO DR. RAY What company puts out Pitressin powder?

DR. RAY I am a little uncertain but I think it is Armour I am surprised that more people don t know about this but it is a very convenient method The powder is in a little capsule and an atomizer is provided with it The end of the capsule is perforated with a pin and the atomizer simply blows the powder out of the capsule

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325 Sullivan E J., 516 Greenleaf Building Jacksonville Florida
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